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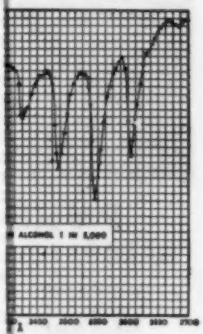

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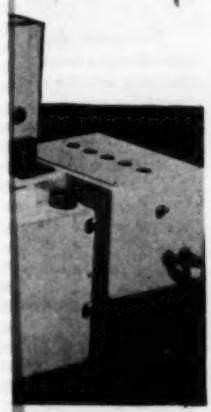

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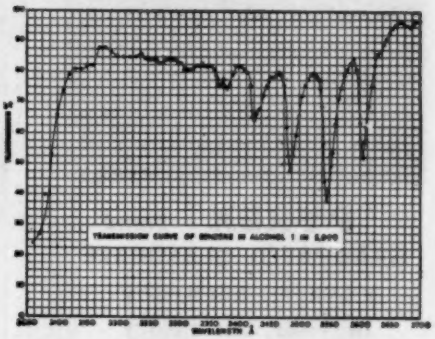

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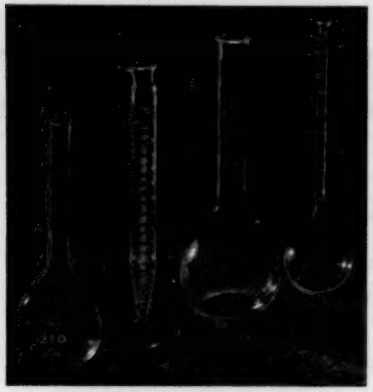

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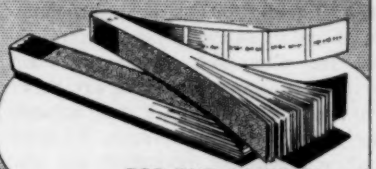

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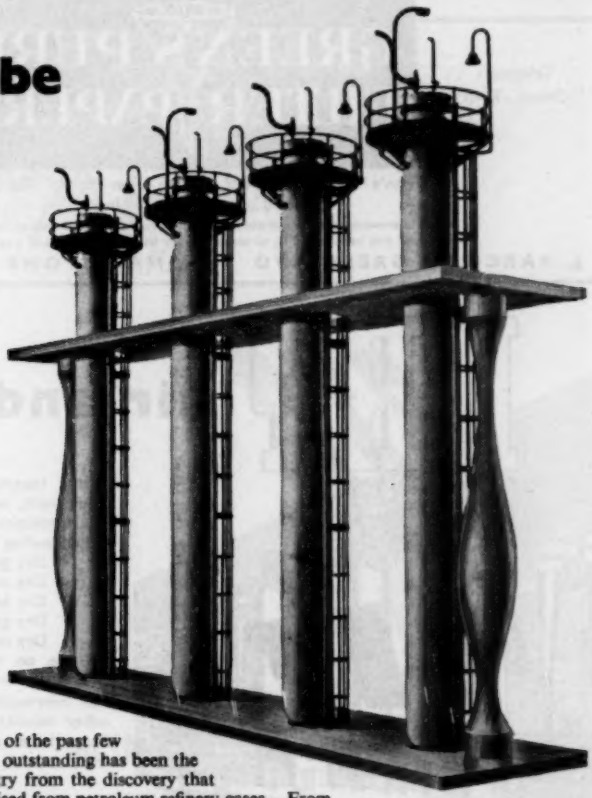

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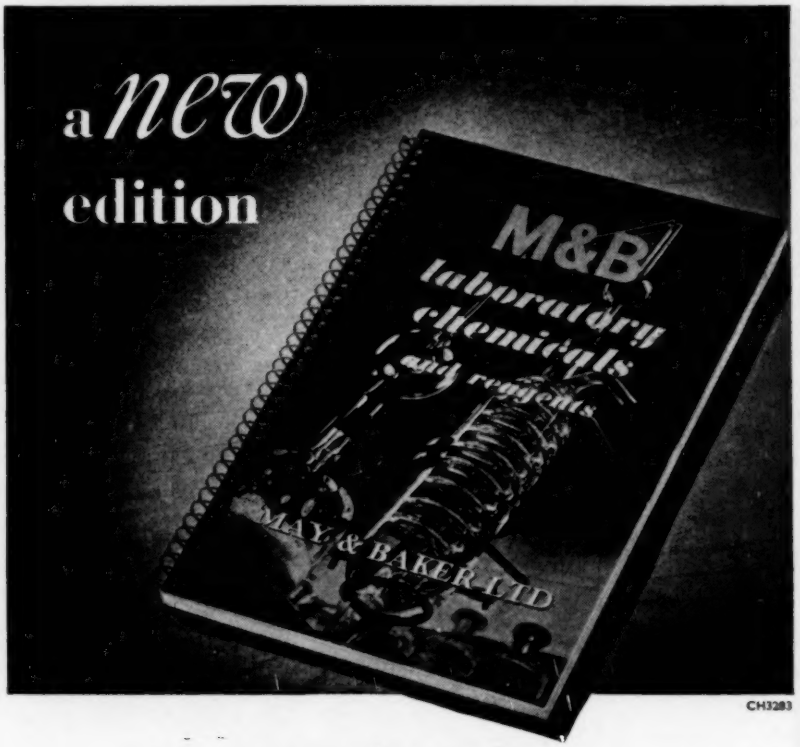

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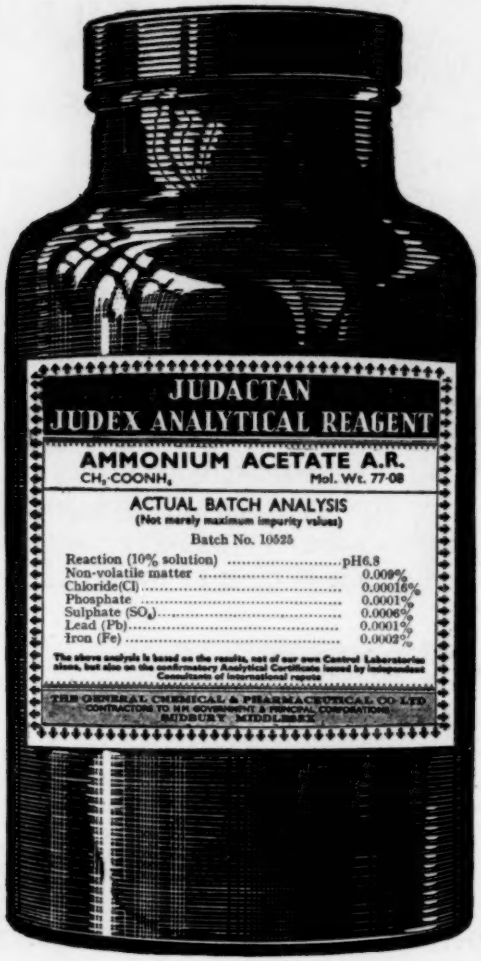
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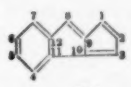
192. *Indene Series. Part I. A Synthesis of* 1 : 2 : 3 : 8-*Tetrahydro*-1-*keto*cyclo*pent*[a]*indene.*

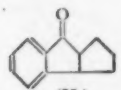
By G. R. Clemo, L. H. Groves, L. Munday, and G. A. Swan.

The ketone named in the title has been prepared by the cyclisation of β-3-indenylpropionic acid (V), obtained (*a*) by a Stobbe condensation with indan-1-one and (*b*) by the malonic ester synthesis from 3-bromomethylindene (X; X = Br). The ketone has been converted into the hexahydrocompound (II), but attempts to prepare *cyclo*pent[*a*]indene have been unsuccessful.

The work described in this and the following papers had, as its main object, the synthesis of the unknown hydrocarbon *cyclo*pent[*a*]indene (I).* Until recently, no simple derivative of (I) was known. However, Baker and Leeds (*J.*, 1948, 974) have described the preparation of the ketone (II), and work begun in this laboratory in 1947 led to the synthesis of the ketone (III) and later of other derivatives.



(I.)



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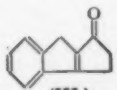
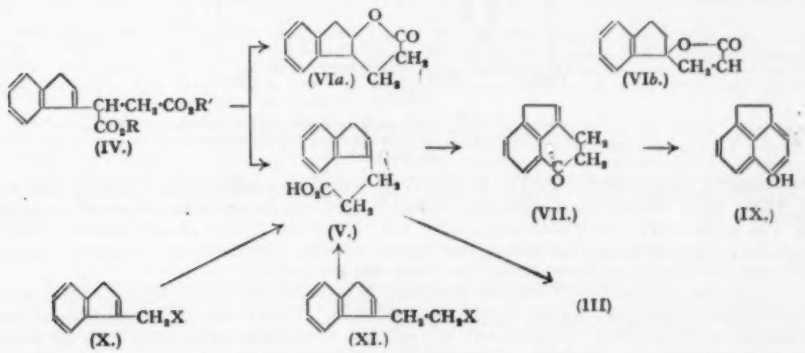


(III.)

Indan-1-one was condensed with ethyl succinate in a modified Stobbe condensation (Johnson, Johnson, and Petersen, *J. Amer. Chem. Soc.*, 1945, **67**, 1360), yielding a half ester which could not be crystallised and probably consisted of a mixture of (IV; R = Et, R′ = H) with the corresponding αβ-unsaturated ester, in which the possibility of geometrical isomerism arises. The crude product was therefore treated with diazomethane, giving (IV; R = Et, R′ = Me) (possibly accompanied by isomers) which was hydrolysed with hydrochloric acid to



β-3-indenylpropionic acid (V) accompanied by the lactone (VI*a* or *b*). The acid appeared to be free from the isomer with an exocyclic double bond, for ozonolysis gave an uncrystallisable acid and no indan-1-one could be obtained. Attempts to hydrolyse the crude Stobbe condensation product without methylation gave unsatisfactory results.

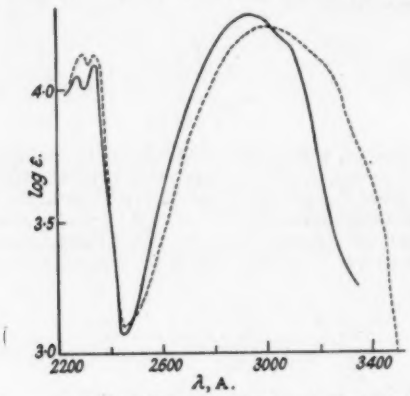
The yield of the acid (V) was low, so other methods of preparation were investigated. By the action of phosphorus tribromide, 3-hydroxymethylindene was converted into the corresponding bromide (X; X = Br), which was condensed with ethyl sodiomalonate, then hydrolysed, and decarboxylated, to yield the acid (V).

3-2′-Hydroxyethylindene (XI; X = OH) was prepared from 3-indenylmagnesium bromide and ethylene oxide. Conversion into the corresponding bromide and cyanide, followed by

* This name and the numbering as in (I), except for the additional numbers (9—12) are those of the Ring Index and not those used in *J.*, 1948, 974.

alkaline hydrolysis, gave (V) in low yield. Hydrolysis of the product of the reaction between indan-1-one, ethyl β-bromopropionate, and magnesium also afforded (V) in very low yield. Unsuccessful attempts were made to synthesise this acid by condensing ethyl β-bromopropionate with (*a*) the sodio-derivative of indene, (*b*) ethyl sodio-2-ketoindane-1-carboxylate, and (*c*) ethyl sodioindene-3-carboxylate (a convenient synthesis of this ester was found in the reaction between the sodio-derivative of indene and ethyl carbonate).

The acid (V) could not be cyclised by zinc chloride–acetic anhydride (Johnson *et al.*, *loc. cit.*). The action of concentrated phosphoric acid or anhydrous hydrogen fluoride gave no recognisable products, but that of concentrated sulphuric acid afforded a product, in yield too small to allow of purification, insoluble in sodium hydrogen carbonate but soluble in sodium hydroxide solution. The melting point of this impure material was *ca.* 110—130°, compared with 126° for 5-hydroxyacenaphthene (IX), which might be formed by cyclisation of (V) to (VII) followed by isomerisation. However, the action of stannic chloride on the acid chloride of (V) yielded 1 : 2 : 3 : 8-tetrahydro-1-keto*cyclo*pent[*a*]indene (III) in 55% yield. That the structure of this ketone is (III) rather than (VII) is indicated by the following facts: (1) The formation of a red 2 : 4-dinitrophenylhydrazone suggests an αβ-unsaturated ketone. The absorption spectrum of this derivative closely resembles that of ethyl styryl ketone (cf. Braude



——— 1 : 2 : 3 : 8-*Tetrahydro*-1-*keto*cyclo*pent*[a]*indene*.
– – – – 1 : 2 : 3 : 4 : 9 : 10-*Hexahydro*-1-*keto*phenanthrene.
(*In ethanol.*)

and Jones, *J.*, 1945, 498). (2) The ketone (VII) would be expected to be readily isomerised to (IX). After being heated with 50% sulphuric acid, the ketone was recovered unchanged. (3) The ultra-violet absorption spectrum of the ketone (see figure) closely resembles that of 1 : 2 : 3 : 4 : 9 : 10-hexahydro-1-ketophenanthrene (Wilds, Beck, Close, Djerassi, Johnson, Johnson, and Shunk, *J. Amer. Chem. Soc.*, 1947, **69**, 1985).

The results obtained by Ponndorf–Meerwein, lithium aluminium hydride, Clemmensen, or Wolff–Kishner reduction of (III) were not encouraging. The substance absorbed two moles of hydrogen in the presence of either Adams's catalyst or palladium–charcoal; but the product was not homogeneous, probably consisting of a mixture of stereoisomers, and attempts to dehydrogenate either it or the ketone yielded no crystalline products. The crude hydrogenation product was therefore dehydrated with phosphoric oxide, the resulting olefin hydrogenated in the presence of palladium–charcoal, and the product (II; CH_2 instead of CO) oxidised by chromic acid to a ketone, the semicarbazone and 2 : 4-dinitrophenylhydrazone of which agreed in properties with those of (II); no depression of melting point occurred on admixture with corresponding specimens prepared by Baker and Leeds's method (*loc. cit.*).

Attempts were also made to prepare a thioketal from (III), which might be expected to yield a hydrocarbon on treatment with Raney nickel. Mixtures of ethane- or toluene-ω-thiol and (III) rapidly developed a purple colour and fluorescence, which, on dilution with benzene, changed to green with a red fluorescence. The colour was discharged by water, but not by concentrated hydrochloric acid, and the ketone could be recovered unchanged. Similar results were obtained with the closely analogous 3 : 4-dihydro-3′-keto-1 : 2-*cyclo*pentenonaphthalene

(Johnson *et al., loc. cit.*). However, with an open-chain analogue, ethyl styryl ketone, the reaction mixture developed only a pale pink colour, and use of ethanethiol in acetic acid containing a small amount of concentrated hydrochloric acid gave a monothio-compound:

$Et\cdot CO\cdot CH_2\cdot CHPh\cdot SEt$	$(EtS)_2CEt\cdot CH{:}CHPh$	$(EtS)_2CEt\cdot CH_2\cdot CHPh\cdot SEt$
(XII.)	(XIII.)	(XIV.)

this is probably (XII) as it possesses ketonic properties, although the 2 : 4-dinitrophenylhydrazone and semicarbazone were oils. Use of ethanethiol in the presence of anhydrous zinc chloride and sodium sulphate gave, as major product, a dithio-compound, probably (XIII) with a small amount of what may be the trithio-compound (XIV).

Experimental.

(All m. p.s are uncorrected.)

Methyl β-Carbethoxy-β-3-indenylpropionate (IV; R = Et, R′ = Me).—Potassium (4·4 g.) was dissolved in dry *tert.*-butyl alcohol (100 ml.), in a three-necked flask fitted with a tap-funnel, reflux condenser with a mercury seal, and a delivery tube which could be connected to either a water pump or a source of pure, dry nitrogen. The solution was cooled in ice, and ethyl succinate (29·0 g.) added. The apparatus was evacuated and filled with nitrogen several times and then the flask was heated in an oil-bath at 110—120°, with nitrogen passing through.

To the boiling solution indan-1-one (15·0 g.) in *tert.*-butyl alcohol (15 ml.) was added during 30 minutes. The solution was heated for a further 10 minutes, then cooled, acidified with 5N-hydrochloric acid (60 ml.), and the solvents removed (reduced pressure). The residue was extracted with ether (5 × 30 ml.), the extracts were filtered, and washed with water, and finally with 10% ammonia solution. The ammoniacal layer, after being washed with ether, was acidified, the precipitated oil was extracted with ether, the extract dried (Na_2SO_4), and the ether removed. The residue, a dark viscous oil (11·6 g.), was dissolved in dry ether (50 ml.), treated with a solution of diazomethane (5·0 g.) in ether (350 ml.) and kept overnight, the ether removed, and the residue distilled, giving (i) methyl ethyl succinate (2·0 g.), b. p. 90—95°/3 mm., 207—208°/750 mm., and (ii) the *indenyl* ester, a straw-coloured oil (4·1 g.), b. p. 208—210°/3 mm. (Found: C, 70·1; H, 6·85. $C_{16}H_{18}O_4$ requires C, 70·1; H, 6·6%). The neutral ethereal extract deposited, when kept, large light-brown needles of 2-indan-1′-ylideneindan-1-one (4·0 g.), m. p. 140—141·5° (lit., 142—143°) (Found: C, 87·9; H, 5·75. Calc. for $C_{18}H_{14}O$: C, 87·8; H, 5·7%); the mother-liquors therefrom were distilled, finally under reduced pressure to remove unchanged indan-1-one, and the residue triturated with light petroleum (b. p. 60—80°) and repeatedly recrystallised from toluene, giving a small amount of yellow solid, m. p. 244—247° [Found: C, 86·35; H, 5·3%; *M* (Rast), 286].

3-Indenylsuccinic Acid.—The ethyl methyl ester (0·3 g.) was heated under reflux with sodium hydroxide solution (10%; 10 ml.) for 6 hours in an atmosphere of nitrogen. The solution was cooled, washed with ether, boiled, cooled, and acidified. The precipitated brown gum soon crystallised. Recrystallisation from dilute ethanol (charcoal) gave the cream-coloured *acid*, m. p. 176·5—180·5° (Found: C, 67·55; H, 5·7. $C_{13}H_{12}O_4$ requires C, 67·25; H, 5·2%).

β-3-Indenylpropionic Acid.—The ethyl methyl ester (IV; R = Et, R′ = Me) (5·1 g.) was heated under reflux with acetic acid (70 ml.), water (30 ml.), and concentrated hydrochloric acid (25 ml.), in an atmosphere of nitrogen for 5 hours. The mixture was evaporated to dryness under reduced pressure and the residue extracted with ether. The extract was washed with water and then with sodium hydrogen carbonate solution. Acidification of the latter gave the *propionic acid* (1·6 g.), separating from aqueous methanol as cream-coloured needles, m. p. 120·5—121·5° (Found: C, 76·9; H, 6·7. $C_{12}H_{12}O_2$ requires C, 76·6; H, 6·4%).

The Lactone (VI*a or* VI*b*).—The neutral ethereal extract from the above experiment was dried (Na_2SO_4) and the ether was removed. A colourless oil remained which crystallised when scratched. Recrystallisation from benzene–light petroleum afforded the *lactone* (0·5 g.) as colourless plates, m. p. 125° (Found: C, 76·0; H, 6·6. $C_{12}H_{10}O_2$ requires C, 76·6; H, 6·4%). On hydrolysis with 10% sodium hydroxide solution (15 ml.) for 1 hour on the water-bath, in an atmosphere of nitrogen, this gave an almost theoretical yield of the acid (V).

Methyl β-Carboxy-β-3-indenylpropionate (IV; R = H, R′ = Me).—Partial hydrolysis of the ethyl methyl ester (IV), *i.e.*, for only 2 hours under reflux gave the *methyl carboxy*-ester (IV; R = H, R′ = Me). It was separated from the crude acid (V) by virtue of its relative insolubility in ether. Recrystallisation from dilute methanol gave light-brown prisms, m. p. 140—141° (Found: C, 67·9; H, 5·6. $C_{14}H_{14}O_4$ requires C, 68·3; H, 5·7%).

1 : 2 : 3 : 8-*Tetrahydro*-1-*keto*cyclo*pent*[a]*indene* (III).—A solution of β-3-indenylpropionic acid (0·2 g.) and phosphorus pentachloride (0·25 g.) in dry benzene (20 ml.) was kept at room temperature for 3 hours, cooled in ice, and treated with stannic chloride (0·8 g.) in benzene (10 ml.), a deep cherry-red solid being deposited immediately. The mixture was kept at room temperature for 2 days, and the complex then decomposed with ice and dilute hydrochloric acid. The aqueous layer was extracted with ether, the ether and benzene layers were combined, washed with dilute hydrochloric acid, water, 10% sodium hydroxide solution, and dried (Na_2SO_4), and the solvents were removed. Recrystallisation from light petroleum (b. p. 60—80°) gave the *ketone* as pale brown needles, m. p. 137—139° (0·1 g.) (Found: C, 84·6; H, 5·85. $C_{12}H_{10}O$ requires C, 84·7; H, 5·9%). Light absorption in ethanol: $\lambda_{max.}$ 2940, 2350, and 2290 A.; log $\varepsilon_{max.}$ = 4·28, 4·10, and 4·05 respectively; $\lambda_{min.}$ 2470 A.; log $\varepsilon_{min.}$ = 3·07.

The *semicarbazone* separated from acetic acid as yellow needles, m. p. 253—254° (decomp.) (Found:

C, 68·4; H, 5·55. $C_{19}H_{13}ON_3$ requires C, 68·7; H, 5·75%). The 2 : 4-*dinitrophenylhydrazone* formed clusters of red needles, m. p. 257—257·5° (decomp.) (from acetic acid) (Found: C, 62·0; H, 4·3. $C_{18}H_{14}O_4N_4$ requires C, 61·7; H, 4·0%). Light absorption in chloroform: $\lambda_{max.}$ 4040 and 3150 A.; log $\varepsilon_{max.}$ = 4·47 and 4·07; $\lambda_{min.}$ 3360 and 2925 A.; log $\varepsilon_{min.}$ = 3·96 and 3·90. Light absorption of ethyl styryl ketone 2 : 4-dinitrophenylhydrazone in chloroform: $\lambda_{max.}$ 3920 and 3050 A.; log $\varepsilon_{max.}$ = 4·43 and 4·17; $\lambda_{min.}$ 3270 and 2850 A.; log $\varepsilon_{min.}$ = 3·97 and 4·05.

Ozonolysis of β-3-Indenylpropionic Acid.—A solution of the acid (0·2 g.) in dry pure ethyl acetate (25 ml.) was ozonised for 1½ hours. After removal of the excess of ozone by evacuation, the mixture was hydrogenated in the presence of palladium–charcoal at atmospheric pressure and temperature. The catalyst was filtered off, the filtrate evaporated (reduced pressure), and the residue dissolved in ether and extracted with sodium hydrogen carbonate solution. The neutral ethereal solution, on evaporation, gave a negligible residue, while the sodium hydrogen carbonate extract on acidification yielded a gummy acid.

Reaction between Ethyl Styryl Ketone and Ethanethiol.—(*a*) A solution of the ketone (6·5 g.), ethanethiol (13 g.), and concentrated hydrochloric acid (0·5 ml.) in acetic acid (60 ml.) was kept at room temperature for 3 days and then distilled, giving *5-ethylthio-5-phenylpentan-3-one* (XII) (7 g.) as a colourless oil, b. p. 143—147°/3 mm. During 24 hours at 0° this formed colourless thick needles, m. p. 33—34° (Found: C, 70·45; H, 8·0; S, 15·0. $C_{13}H_{18}OS$ requires C, 70·25; H, 8·1; S, 14·4%).

(*b*) A mixture of the ketone (2·1 g.), freshly fused zinc chloride (2·5 g.), and anhydrous sodium sulphate (2·5 g.) was cooled in ice, treated slowly with ethanethiol (4·0 g.), and kept at room temperature for 4 days during which a deep red colour developed. Water was added, the mixture extracted with chloroform, the extract dried (Na_2SO_4), and the solvent removed. Light petroleum (b. p. 40—60°) was added to the residue, a white solid (0·15 g.) of indeterminate m. p. (60—65°), containing sulphur was filtered off, the filtrate evaporated, and the residue distilled. 3 : 3-*Diethylthio-1-phenylpent-1-ene* (XIII) (1·5 g.), b. p. 130—132°/3 mm., formed a colourless oil (Found: C, 68·1; H, 8·05; S, 25·3. $C_{15}H_{22}S_2$ requires C, 67·7; H, 8·25; S, 24·1%).

3-Bromomethylindene.—Phosphorus tribromide (7·7 g.) in dry benzene (50 ml.) was added slowly to a solution of 3-hydroxymethylindene (10 g.) (Grignard and Courtot, *Compt. rend.*, 1915, **160**, 501; *Ann. Chim.* 1915, [ix], **4**, 95) in benzene (50 ml.). The mixture was kept overnight at room temperature, then treated with ice, the benzene layer washed with sodium carbonate solution and dried (Na_2SO_4), the benzene removed under reduced pressure at 35—40°, and the residue distilled, not more than 4 g. at a time, giving unchanged 3-hydroxymethylindene (1·0 g.), b. p. 100—125°/2 mm., and the required *bromide* (4·1 g.), b. p. 125—135°/2 mm., a yellow unstable lachrymatory oil (Found: Br, 38·2. $C_{10}H_9Br$ requires Br, 38·3%). This compound is unstable to heat but, unless distilled, it was unsatisfactory for the next stage of our work.

Ethyl α-Carbethoxy-β-3-indenylpropionate.—To a solution of sodium (0·3 g.) in absolute ethanol (10 ml.) were added first ethyl malonate (2·2 g.), then a solution of 3-bromomethylindene (2·8 g.) in ethanol (10 ml.). The mixture was heated at 50° for 6 hours and then on the water-bath for a further 12 hours, the bulk of the ethanol removed by distillation, and the residue treated with water. The mixture was extracted with ether, and the extracts were washed (water), dried ($CaCl_2$), and distilled, finally under reduced pressure, affording the *ester* as a straw-coloured oil (2·95 g.), b. p. 164—166°/2 mm. (Found: C, 71·1; H, 7·4. $C_{17}H_{20}O_4$ requires C, 70·8; H, 6·95%).

This ester (3·45 g.) was heated under reflux for 1 hour with a solution of potassium hydroxide (4 g.) in ethanol (15 ml.), and the bulk of the ethanol then removed by distillation. The residue was dissolved in water, and the solution extracted with ether, boiled, and acidified with dilute hydrochloric acid, the *acid* (2·7 g.) separating as light brown crystals, m. p. 181—182° (decomp.) (Found: C, 67·1; H, 5·5. $C_{13}H_{12}O_4$ requires C, 66·95; H, 5·55%).

β-3-Indenylpropionic Acid.—The foregoing acid (4·9 g.) was heated at 185° (oil-bath) for 3—4 minutes until evolution of carbon dioxide ceased. The cooled residue, recrystallised twice from aqueous methanol, had m. p. 118—120° (3·3 g.).

3-2′-Hydroxyethylindene.—A suspension of 3-indenylmagnesium bromide in ether (30 ml.), prepared from indene (10 g.) (Grignard, *Compt. rend.*, 1911, **152**, 273), was cooled in ice, and ethylene oxide (5 g.) in ether (10 ml.) was added dropwise. When the vigorous reaction had subsided, the ether was removed by distillation and the residue heated at 100° for 1 hour, cooled, and decomposed with ice and dilute hydrochloric acid; the organic layer was separated and the aqueous portion extracted with ether. The combined organic extracts were washed with sodium carbonate solution, then dried (Na_2SO_4), the ether removed by distillation, and the residue fractionated under reduced pressure, giving unchanged indene (5 g.), b. p. 80—90°/15 mm., and the *alcohol*, a pale yellow oil (3·7 g.), b. p. 168—170°/15 mm. (Found: C, 82·55; H, 7·4. $C_{11}H_{12}O$ requires C, 82·5; H, 7·5%).

3-2′-Bromoethylindene.—The above alcohol (1·0 g.), phosphorus tribromide (0·77 g.), and benzene (10 ml.) were heated at 50° for 8 hours and then kept overnight at room temperature. The mixture was decomposed with water, the benzene layer washed with sodium carbonate solution and dried (Na_2SO_4), and the benzene removed at 35—40°. The residue was distilled, affording a yellow *bromide* (0·55 g.), b. p. 117—120°/3 mm. (Found: C, 59·4; H, 5·3; Br, 35·8. $C_{11}H_{11}Br$ requires C, 59·2; H, 4·95; Br, 35·85%).

β-3-Indenylpropionic Acid.—The above bromide (1·55 g.) in ether–ethanol (2 : 5) was added to sodium cyanide (0·5 g.) in water (0·6 ml.). The mixture was left at room temperature overnight and then heated on the water-bath for 4 hours, treated with water, and extracted with ether. The extracts were dried (Na_2SO_4), the ether was removed, and the residue distilled, giving a pale yellow oil, b. p. 120°/3 mm. (0·6 g.). This cyanide in 15% aqueous-ethanolic sodium hydroxide (0·75 g.) was heated under reflux for 5 hours on the water-bath. Most of the ethanol was removed, and the solution diluted with water,

washed with ether, boiled with charcoal, filtered, cooled, and acidified (dilute hydrochloric acid). The product (V) (0·1 g.), after recrystallisation from dilute methanol, had m. p. 119—121°, not depressed by admixture with a specimen prepared as above.

Reaction between Indan-1-one and Ethyl β-Bromopropionate.—A mixture of ethyl β-bromopropionate (6 g.), indan-1-one, (4·4 g.), magnesium shavings (0·8 g.), and toluene (4 ml.) was heated under reflux for 4 hours, cooled, filtered, and treated with ice and dilute sulphuric acid. The organic layer was separated, then dried (Na_2SO_4), and the solvent removed. The residue was boiled with a solution of potassium hydroxide (5 g.) in water (5 ml.) and ethanol (10 ml.) for 2 hours. The mixture was cooled, diluted with water, and washed with ether. The aqueous layer was acidified (dilute hydrochloric acid) and extracted with ether, the extracts were dried (Na_2SO_4), and the solvent removed, leaving a dark red oil (2·0 g.) which was distilled, giving the required acid (0·3 g.), b. p. (bath-temp.) 240°/2 mm., m. p. 118—120°, not depressed on admixture with (V) obtained as above.

Ethyl Indene-3-carboxylate.—To sodamide prepared from sodium (4·1 g.) in liquid ammonia (140 ml.) (Levine and Hauser, *J. Amer. Chem. Soc.*, 1944, **66**, 1768), indene (10 g.) in dry ether (40 ml.) was added during 15 minutes. The mixture was warmed on the water-bath, dry ether being added to maintain a constant volume. When all the ammonia had evaporated, ethyl carbonate (20 g.) was added slowly, the mixture was heated under reflux (water-bath) for 3½ hours, and poured on crushed ice (150 g.) and acetic acid (15 ml.). The ethereal layer was separated, washed three times with saturated sodium hydrogen carbonate solution, dried (Na_2SO_4), and distilled, first at atmospheric pressure to remove the excess of ethyl carbonate (8 g.) and then under reduced pressure, affording unchanged indene (4 g.), b. p. 75—85°/15 mm., and the required ester (6·2 g.), b. p. 155°/15 mm. Alkaline hydrolysis gave indene-3-carboxylic acid, m. p. 156—157° (not depressed on admixture with an authentic specimen).

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-8-*keto*cyclo*pent*[a]*indene* (II).—The ketone (III) (1·45 g.), hydrogenated in glacial acetic acid at room temperature and atmospheric pressure over Adams's catalyst, absorbed 2 mols. of hydrogen. The crude product was dehydrated with phosphoric oxide (2·5 g.) in benzene (20 ml.) under reflux (2½ hours). The olefin, thus obtained as an almost colourless oil (0·51 g.), b. p. 120—125°/20 mm., was hydrogenated in ethanol in presence of palladium–charcoal, 1 mol. of hydrogen being absorbed. The crude product obtained by filtration and removal of the solvent was heated on the water-bath for 3 hours with sodium dichromate (1·5 g.) and acetic acid (5 ml.). The solvent was removed (reduced pressure), water added, and the mixture extracted with ether. The extract was dried (Na_2SO_4) and fractionated, giving unchanged 1 : 2 : 3 : 8 : 9 : 10-hexahydro*cyclo*pent[*a*]indene (0·2 g.), a colourless oil, b. p. (bath-temp.) 135—145°/15 mm., and the ketone (II) (0·15 g.), a colourless oil, b. p. (bath-temp.) 170—180°/15 mm.

The 2 : 4-dinitrophenylhydrazone of (II) separated from acetic acid as dark red needles, m. p. 215—216°, not depressed on admixture with an authentic specimen (lit., 216—217°) (Found : C, 61·15; H, 4·8. Calc. for $C_{18}H_{16}O_4N_4$: C, 61·4; H, 4·55%). The semicarbazone separated from ethanol as colourless plates, m. p. 242° (decomp.), not depressed on admixture with an authentic specimen [lit., 242° (decomp.)] (Found : C, 68·1; H, 6·6. Calc. for $C_{13}H_{15}ON_3$: C, 68·1; H, 6·55%).

The light-absorption data were determined by use of a Hilger Medium Quartz Spectrograph.

Thanks are offered to Imperial Chemical Industries Limited, Billingham, and to Middlesbrough Education Committee for the award of scholarships (to L. M.), and to the Department of Scientific and Industrial Research for a maintenance grant (to L. H. G.).

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[*Received, October 21st*, 1950.]

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193. *Indene Series. Part II. A Synthesis of* 1 : 2 : 3 : 4 : 9 : 10-*Hexahydro*-2-*keto*cyclo*pent*[a]*indene.*

By L. H. GROVES and G. A. SWAN.

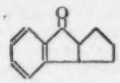
The ketone (I) named in the title has been synthesised and converted into 1 : 2 : 3 : 8 : 9 : 10-hexahydro*cyclo*pent[*a*]indene (I; CH_2 instead of CO), but attempts to prepare *cyclo*pent[*a*]indene from it or related substances failed.

IN view of the low yield obtained in the syntheses of 1-keto-1 : 2 : 3 : 8-tetrahydro*cyclo*pent[*a*]-indene * described in Part I (preceding paper), the 2-ketohexhydro-derivative (I) has now been prepared (cf. the synthesis of *cis*-β-*bicyclo*octanone by Linstead and Meade, *J.*, 1934, 935).

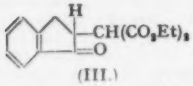
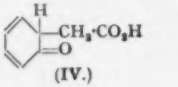
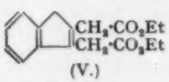
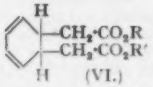
2-Bromoindan-1-one was condensed with ethyl sodiomalonate, to give ethyl 1-keto-2-indanylmalonate (III), which on hydrolysis and decarboxylation yielded the keto-acid (IV). The derived ethyl ester was subjected to the Reformatsky reaction with ethyl bromoacetate

* See footnote, p. 863.

and then distilled: the product probably consisted of a mixture of the indene derivative (V) with the indane isomer containing an exocyclic double bond at position 1. A small amount of

(I.)  (II.)

a lactone was also obtained, and this underwent hydrogenolysis in the presence of palladium charcoal to the half-ester (VI; R = H, R′ = Et) which on esterification gave ethyl indane-1 : 2-diacetate (VI; R = R′ = Et). The mixture of unsaturated esters was also hydrogenated

 (III.)  (IV.)  (V.)  (VI.)

to this ester (VI; R = R′ = Et), which by Dieckmann cyclisation, followed by hydrolysis yielded 2-keto-1 : 2 : 3 : 8 : 9 : 10-hexahydro-2-keto*cyclo*pent[*a*]indene (I) in 64% yield. The ester (VI; R = R′ = Et) was also hydrolysed to the dibasic acid which on distillation with barium hydroxide at 330—365° gave the same ketone (I).

This ketone was reduced to the corresponding secondary alcohol by lithium aluminium hydride, and dehydration then yielded a liquid olefin, probably a mixture of 1 : 8 : 9 : 10- and 3 : 8 : 9 : 10-tetrahydro*cyclo*pent[*a*]indene. This was recovered unchanged after passage (in the vapour phase) over palladium–charcoal at 330°. Attempts were also made to dehydrogenate it in the liquid phase by palladium, sulphur, selenium, and chloranil, and also by bromination (with bromine or *N*-bromosuccinimide) followed by dehydrobromination (with pyridine, collidine, potassium acetate, etc.). In all cases, either the olefin was recovered unchanged, or black polymeric products resulted.

The ketone (I) was reduced by the Clemmensen method to 1 : 2 : 3 : 8 : 9 : 10-hexahydro-*cyclo*pent[*a*]indene (I; CH_2 instead of CO). This hydrocarbon did not give a crystalline nitro-derivative, but the structure was confirmed by oxidation with chromic acid to ketone (II) (Baker and Leeds, *J.*, 1948, 974).

Diethyl indane-2-acetate-1-cyanoacetate was also synthesised, as it was hoped that it might provide an alternative route to the diester (VI; R = R′ = Et), but the yield was low.

The polymeric products resulting from attempts to prepare *cyclo*pent[*a*]indene may be due to its fulvene-like structure. As the introduction of a methyl group at position 8 might be expected to increase the stability of the fulvene structure somewhat (cf. Thiele, *Ber.*, 1900, **33**, 666), the synthesis of 8-methyl*cyclo*pent[*a*]indene was attempted. The ketone (II) was allowed to react with methylmagnesium iodide and the product, after dehydration, was treated first with *N*-bromosuccinimide, then with pyridine; but, as before, polymeric products resulted. The ketone (I) was similarly treated with phenylmagnesium bromide, but attempts to dehydrogenate the resulting olefin with palladium or selenium led to polymerisation.

Experimental.

(All m. p.s are uncorrected.)

Ethyl 1-*Keto*-2-*indanylmalonate* (III).—Indan-1-one (19 g.) in dry ether (150 ml.) was treated dropwise at 10° with bromine (22·9 g.), the solution being stirred briskly, and each drop of bromine was allowed to be decolorised before the next drop was added. The mixture was then stirred at room temperature so that any precipitate formed was dissolved, then poured on ice, the ethereal layer separated, washed with sodium carbonate solution, and dried (Na_2SO_4), and the ether removed by distillation, leaving crude 2-bromoindan-1-one. A solution of this in dry benzene (20 ml.) was added slowly, with external cooling, to a suspension of ethyl sodiomalonate [prepared from ethyl malonate (25 g.) and powdered sodium (2·31 g.) in dry benzene (70 ml.)]. The mixture was heated under reflux on the water-bath for 18 hours, cooled, and diluted with water, and the benzene layer separated, washed with water, dried (Na_2SO_4), and distilled, giving the crude *ester* (26·4 g.), b. p. 188—210°/2 mm. Redistillation afforded a pale yellow oil, b. p. 190—193°/2 mm. (Found: C, 66·05; H, 6·5. $C_{16}H_{18}O_5$ requires C, 66·1; H, 6·2%).

1-*Keto*-2-*indanylmalonic Acid*.—The crude ester (III) (27·8 g.), potassium hydroxide (28 g.), and alcohol (120 ml.) were heated under reflux for 1 hour, the bulk of the alcohol removed (reduced pressure), and water (100 ml.) added. The dark solution was filtered, extracted three times with ether, boiled, cooled in ice, and acidified (dilute hydrochloric acid). A small amount of precipitated tar was filtered off, the filtrate was extracted with ether, the extracts were dried (Na_2SO_4), and the ether was removed by distillation, the *acid* remaining as an oil, which set to a colourless solid (20·9 g.), m. p. 164—165° (decomp.) (Found: C, 61·2; H, 4·7. $C_{12}H_{10}O_5$ requires C, 61·55; H, 4·3%).

1-*Keto*-2-*indanylacetic Acid*.—The foregoing acid was quantitatively decarboxylated at 170° (oil-bath) (until gas evolution ceased). The *acetic acid* crystallised, on cooling, to a light brown solid, m. p. 143—146°, and separated from dilute methanol as almost colourless needles, m. p. 147—148° (Found: C, 69·25; H, 5·5. $C_{11}H_{10}O_3$ requires C, 69·45; H, 5·25%).

Absolute ethanol (60 ml.), containing the acid (15·6 g.), was saturated at 0° with dry hydrogen chloride, and heated under reflux for 5 hours. The bulk of the ethanol was removed by distillation, and the mixture diluted with water and extracted with ether. The extract was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and distilled, giving the *ethyl* ester (16·2 g.) as a pale yellow oil, b. p. 155°/2 mm., which on cooling formed pale yellow crystals, m. p. 39—41° (Found: C, 71·2; H, 6·65. $C_{13}H_{14}O_3$ requires C, 71·55; H, 6·4%). Acidification of the sodium hydrogen carbonate extract gave unchanged acid (1·0 g.).

Reformatsky Reaction between Ethyl Bromoacetate and Ethyl 1-*Keto*-2-*indanylacetate*.—(*a*) The keto-ester (10 g.), ethyl bromoacetate (8·45 g.), zinc wool (5·9 g.), dry benzene (40 ml.), and a particle of iodine were heated on the water-bath until a vigorous reaction started, then removed from the water-bath until this had subsided, and finally heated under reflux for 10 minutes. The mixture was cooled, poured into ice-cold 10% sulphuric acid, and the benzene layer was washed with water and then with sodium carbonate solution, dried (Na_2SO_4), and distilled. The pale yellow oil of boiling range 185—210°/3 mm. (9·1 g.) was a mixture of the olefinic ester (V) and its isomer.

(*b*) When the time of heating was increased to 45 minutes, two fractions were obtained: (i) a colourless oil (7·9 g.), b. p. 185—210°/3 mm., redistillation of which afforded the analytically pure mixture of olefinic esters, b. p. 188—190°/3 mm. (Found: C, 70·65; H, 7·05. Calc. for $C_{17}H_{20}O_4$: C, 70·8; H, 6·95%); and (ii) a viscous yellow *lactone* (1·3 g.), b. p. 228—230°/3 mm., which solidified on cooling and separated from benzene–light petroleum (b. p. 60—80°) as colourless silky needles, m. p. 86° (Found: C, 68·8; H, 6·05. $C_{13}H_{14}O_4$ requires C, 69·2; H, 6·15%).

Diethyl Indane-1 : 2-*diacetate* (VI; R = R′ = Et).—(*a*) The product from the Reformatsky reaction (*a*) or [*b*(i)] above (36 g.) in absolute ethanol (120 ml.) was hydrogenated at atmospheric temperature and pressure (10 hours) in presence of 10% palladium–charcoal (4 g.). After removal of the catalyst, the solution was saturated at 0° with dry hydrogen chloride and heated under reflux for 6 hours. The bulk of the ethanol was removed, and the mixture was diluted with water and extracted with ether. The extracts were washed several times with sodium carbonate solution, dried (Na_2SO_4), and distilled, giving the saturated *diester* (32 g.) as a colourless oil, b. p. 185—195°/3 mm. Redistillation gave the pure ester, b. p. 188°/3 mm. (Found: C, 70·3; H, 7·4. $C_{17}H_{22}O_4$ requires C, 70·35; H, 7·6%).

(*b*) Hydrogenation of the lactone (4·3 g.) in ethanol with palladium–charcoal, followed by esterification, yielded the diester (3·0 g.), b. p. 188°/3 mm.

Indane-1 : 2-*diacetic Acid* (VI; R = R′ = H).—The above ester (1 g.) was heated under reflux for 2 hours with potassium hydroxide (1 g.) in ethanol (5 ml.). The mixture was diluted with water, washed with ether, boiled, cooled, and acidified with dilute hydrochloric acid, precipitating the *acid* (0·7 g.), which after two recrystallisations from hot water had m. p. 146°, forming colourless prisms (Found: C, 66·35; H, 5·75. $C_{13}H_{14}O_4$ requires C, 66·65; H, 6·0%).

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-2-*keto*cyclo*pent*[a]*indene* (I).—(*a*) A mixture of the diester (VI; R = R′ = Et) (2·7 g.), benzene (5 ml.), and sodium ethoxide (from sodium, 0·25 g.) was heated (water-bath) for 7 hours, cooled, acidified with concentrated hydrochloric acid (40 ml.), and then heated (water-bath) for a further 12 hours. It was cooled, diluted with water, and extracted with ether, and the extract washed with dilute sodium hydroxide solution, dried (Na_2SO_4), and distilled, affording the *ketone* as a pale yellow oil (1·0 g.), b. p. 135—140°/3 mm. This was purified by heating its semicarbazone with a 50% solution of oxalic acid in water under reflux for 3 hours; it then formed an almost colourless oil, b. p. 131°/2 mm. (Found: C, 83·55; H, 7·4. $C_{13}H_{12}O$ requires C, 83·7; H, 7·0%).

The *semicarbazone* separated as colourless needles (from dilute ethanol), m. p. 200—201° (Found: C, 68·2; H, 6·3. $C_{14}H_{15}ON_3$ requires C, 68·15; H, 6·55%). The 2 : 4-*dinitrophenylhydrazone* separated as orange needles (from ethanol), m. p. 174° (Found: C, 61·5; H, 4·2. $C_{19}H_{16}O_4N_4$ requires C, 61·4; H, 4·55%).

(*b*) A mixture of the acid (VI; R = R′ = H) (0·44 g.) and barium hydroxide (0·09 g.) was heated at 330—365° for 20 minutes. The distillate was extracted with ether and dried (Na_2SO_4) and the ether removed. The residue was distilled under reduced pressure, giving the ketone as a pale yellow oil (0·14 g.), b. p. (bath-temp.) 155—160°/3 mm. The semicarbazone was formed in quantitative yield, m. p. 200° not depressed on admixture with the semicarbazone of the ketone formed as in (*a*).

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-2-*hydroxy*cyclo*pent*[a]*indene*.—The ketone (I) (2·65 g.) in absolute ether (22 ml.) was added dropwise to a solution of lithium aluminium hydride (0·3 g.) in ether (35 ml.). After the reaction had subsided, the mixture was kept at room temperature for 15 minutes and finally heated under reflux for 15 minutes. Water was added cautiously, the mixture acidified with dilute sulphuric acid, and the ethereal layer separated, dried (Na_2SO_4), and distilled, giving the *alcohol* as a colourless oil (2·35 g.), b. p. 144—146°/3 mm. (Found: C, 82·4; H, 8·0. $C_{13}H_{14}O$ requires C, 82·75; H, 8·05%).

Dehydration. The alcohol (2·35 g.) and phosphoric oxide (3 g.) in dry benzene (16 ml.) were heated under reflux for 2½ hours, cooled, and treated with water, and the benzene layer was separated. The aqueous layer was extracted several times with ether. The combined organic extracts were washed with sodium carbonate solution, dried (Na_2SO_4), and fractionated. The olefinic mixture was obtained as a colourless mobile oil (1·62 g.), b. p. 115°/15 mm. (Found: C, 92·1; H, 8·0. Calc. for $C_{13}H_{12}$: C, 92·3; H, 7·7%).

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*cyclo*pent*[a]*indene*.—Amalgamated zinc (4·0 g.), the ketone (I) (1·0 g.), and 1 : 1 hydrochloric acid (4 ml.) were heated under reflux for 24 hours; 1 ml. of concentrated hydrochloric acid was added each 6 hours. The mixture was cooled, diluted with water, and extracted with ether. The extract was dried (Na_2SO_4) and distilled, affording the *hydrocarbon* (0·65 g.) as a colourless mobile oil, b. p. 118—120°/20 mm. (Found: C, 91·4; H, 9·0. $C_{13}H_{14}$ requires C, 91·15; H, 8·85%).

1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-8-*keto*cyclo*pent*[a]*indene* (II).—The above hydrocarbon (2·9 g.) in acetic acid (5 ml.) was added slowly to chromium trioxide (3·6 g.) in 80% acetic acid (15 ml.). The mixture was left for 1 week at room temperature. *iso*Propyl alcohol was added, the solvents were removed (reduced pressure), the residue was treated with water, and the mixture extracted with ether. The extract was washed with sodium hydrogen carbonate solution, dried (Na_2SO_4), and distilled, giving unchanged hydrocarbon (0·9 g.), b. p. 115—116°/15 mm., and the ketone (1·0 g.) as an almost colourless oil, b. p. 150—153°/15 mm. The 2 : 4-dinitrophenylhydrazone was obtained as scarlet needles (from acetic acid), m. p. 216—217° (not depressed on admixture with an authentic sample) and the semicarbazone as colourless plates (from ethanol), m. p. 240—242° (decomp.) (not depressed on admixture with an authentic sample).

*Attempted Dehydrogenation of Tetrahydro*cyclo*pent*[a]*indene*.—The olefin (0·6 g.) was allowed to pass through the apparatus described by Nunn and Rapson (*J.*, 1949, 825) during 1 hour at 330°. 0·4 G. was recovered unchanged.

Grignard Reaction between (I) *and Phenylmagnesium Bromide*.—(a) 1 : 8 : 9 : 10(? 3 : 8 : 9 : 10)-*Tetrahydro*-2-*phenyl*cyclo*pent*[a]*indene*. The ketone (I) (0·3 g.) in ether (7 ml.) was added to a stirred and cooled Grignard solution prepared from magnesium (0·15 g.) and bromobenzene (0·91 g.). The mixture was heated under reflux for ½ hour and kept overnight at room temperature. Water and then dilute hydrochloric acid were added and the mixture was extracted with ether, and the extracts were dried (Na_2SO_4) and distilled, giving a pale yellow oil (0·24 g.), b. p. (bath-temp.) 180—200°/2 mm., which later solidified. Recrystallisation from methanol afforded the *tetrahydro*-2-*phenyl* compound as colourless stubby prisms, m. p. 117·5—118° (Found: C, 92·8; H, 7·15. $C_{19}H_{18}$ requires C, 93·1; H, 6·9%).

(b) 1 : 2 : 3 : 8 : 9 : 10-*Hexahydro*-2-*hydroxy*-2-*phenyl*cyclo*pent*[a]*indene*. In an experiment on a larger scale (1·84 g. of ketone), a liquid *carbinol* (2·16 g.), b. p. 185°/2 mm., was obtained. It solidified on cooling, and recrystallisation from light petroleum (b. p. 40—60°) gave colourless crystals, m. p. 75·5—76·5° (Found: C, 85·9; H, 7·5. $C_{19}H_{18}O$ requires C, 86·4; H, 7·2%).

The carbinol (1·6 g.) was dehydrated with phosphoric oxide (1·38 g.) in benzene (20 ml.) by heating the mixture under reflux for 3 hours. The olefin (1·2 g.), m. p. 115—117°, was obtained.

2-*Indanylacetic Acid*.—1-Keto-2-indanylacetic acid (1·0 g.), amalgamated zinc (4·0 g.), concentrated hydrochloric acid (6 ml.), and toluene (2 ml.) were heated under reflux for 24 hours, concentrated hydrochloric acid (1 ml.) being added after each 6 hours. The cooled mixture was diluted with water and extracted with ether, the extracts were dried (Na_2SO_4), and the solvent was removed, leaving the crude *acid* (0·7 g.) as light brown crystals, m.p. 84—86°. After being twice recrystallised from dilute methanol it afforded fine colourless needles, m. p. 91—92° (Found: C, 74·7; H, 7·0. $C_{11}H_{12}O_2$ requires C, 75·0; H, 6·8%).

Diethyl Indane-2-*acetate*-1-*cyanoacetate*.—The keto-ester (IV) (3·4 g.) and ethyl cyanoacetate (1·77 g.) were added to a solution of potassium (0·64 g.) in absolute ethanol (10 ml.), and the mixture was kept at room temperature for 1 week, diluted with water, acidified with dilute hydrochloric acid, and extracted with ether. The extract was washed with sodium carbonate solution, dried (Na_2SO_4), and distilled. Half of the original materials was recovered together with 0·8 g. of a light brown viscous oil, b. p. 195—205°/3 mm., which, on cooling, nearly all solidified; after recrystallisation from dilute ethanol the *product* formed colourless prisms, m. p. 105—106° (Found: C, 68·6; H, 6·2. $C_{18}H_{19}O_4N$ requires C, 69·0; H, 6·1%).

Reaction between 1 : 8 : 9 : 10(? 3 : 8 : 9 : 10)-*Tetrahydro*cyclo*pent*[a]*indene and N-Bromosuccinimide*.—The olefin (0·55 g.), *N*-bromosuccinimide (0·63 g.), dibenzoyl peroxide (5 mg.), and carbon tetrachloride (5 ml.) were heated under reflux for 1 hour, cooled, and filtered. To the filtrate was added *N*-bromosuccimide (0·63 g.) and dibenzoyl peroxide (5 mg.), and the mixture refluxed for a further ½ hour. It was then filtered, the filtrate washed with sodium hydrogen carbonate solution and dried (Na_2SO_4), and the solvent removed, leaving a dark non-crystalline viscous gum (1·1 g.), containing halogen. This was kept in dry pyridine (5 ml.) for a week at room temperature, depositing a black amorphous powder, which was filtered off. The solution was acidified with dilute hydrochloric acid and extracted with ether, the extract dried (Na_2SO_4), and the solvent removed, leaving a negligible residue.

Reaction between Methylmagnesium Iodide and (II).—To a Grignard solution from methyl iodide (4·5 g.; 300% excess) the ketone (1·9 g.) in dry ether (10 ml.) was added slowly. The mixture was heated (water-bath) for ½ hour, decomposed with ice and dilute hydrochloric acid, and extracted with ether, the ether extracts were washed with water, dried (Na_2SO_4), and distilled. The product (1·2 g.), b. p. 138—140°/18 mm., was heated under reflux for 2 hours with phosphoric oxide (1·5 g.) in benzene (15 ml.) and treated with water, and the benzene layer separated, dried (Na_2SO_4) and distilled, giving an *olefin* as a colourless oil, b. p. 138—140°/18 mm. (Found: C, 91·5; H, 8·35. $C_{13}H_{14}$ requires C, 91·75; H, 8·25%).

Thanks are offered to the Department of Scientific and Industrial Research for a maintenance grant (to L. H. G.), and to Professor G. R. Clemo, F.R.S., for his interest.

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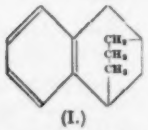
[*Received, October 21st*, 1950.]

194. *Indene Series. Part III. The Cyclisation of* 1-*Benzyl*cyclo*pentene and Isomeric Compounds.*

By L. H. Groves and G. A. Swan.

1- and 2-Benzyl*cyclo*pentanol and α-hydroxybenzyl*cyclo*pentane have been dehydrated, and the resulting olefins cyclised, but the only saturated hydrocarbon isolated was 1 : 3-*endo*ethylene-1 : 2 : 3 : 4-tetrahydronaphthalene.

Cyclisation of the dehydration product of 1-benzyl*cyclo*pentanol was investigated as a possible route to the *cyclo*pent[*a*]indene ring system. Cook and Hewett (*J.*, 1936, 62) have shown the dehydration product of benzyl*cyclo*hexanol to cyclise to give the bridged-ring compound (I),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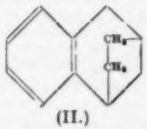
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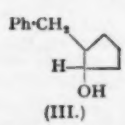
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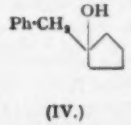
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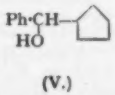
(V.)

rather than the isomeric fluorene derivative; and our results in the benzyl*cyclo*pentanol series have been analogous—cyclisation occurs to give (II) rather than hexahydro*cyclo*pent[*a*]indene.

2-Benzyl*cyclo*pentanol (III), prepared by reduction of 2-benzyl- (Baker and Leeds, *J.*, 1948, 974) or 2-benzylidene-*cyclo*pentanone, was dehydrated with phosphoric oxide and the resulting olefin cyclised by aluminium chloride. The saturated hydrocarbon obtained was, however, 1 : 3-*endo*ethylene-1 : 2 : 3 : 4-tetrahydronaphthalene [*tricyclo*(5 : 4 : $1^{2,6}$)dodeca-7 : 9 : 11-triene] (II), as on chromic acid oxidation it yielded 1 : 3-*endo*ethylene-1 : 2 : 3 : 4-tetrahydro-4-ketonaphthalene (Baker and Leeds, *loc. cit.*).

Dehydration of 1-benzyl*cyclo*pentanol (IV) and cyclisation of the product gave mainly the same product (II), although nitration then yielded a dinitro-derivative in about 10% yield, while no nitro-derivatives could be obtained from the saturated hydrocarbons from (III) or (V). The ultra-violet absorption of the olefin from (IV) suggested that about 10% of the olefin mixture had the double bond conjugated with the benzene ring.

α-Hydroxybenzyl*cyclo*pentane (V) has previously been obtained in low yield by Edwards and Reid (*J. Amer. Chem. Soc.*, 1930, **52**, 3325) by interaction of *cyclo*pentylmagnesium bromide and benzaldehyde. We prepared it by the reduction (by potassium ethoxide in ether) of benzoyl*cyclo*pentane, obtained by the condensation of benzene and *cyclo*pentanecarboxyl chloride. The carbinol (V) was dehydrated with phosphoric oxide and the olefin mixture again appeared to have about 10% of the conjugated isomer; (II) was the only product isolated after cyclisation.

Use of anhydrous oxalic acid instead of phosphoric oxide for the dehydrations gave the same results, except that in the case of the olefin from (V) cyclisation followed by oxidation yielded no recognisable product. Here, however, the ultra-violet absorption indicated that nearly all the olefin mixture had the double bond conjugated with the benzene nucleus.

Catalytic dehydrogenation of (II) with palladium at 255° yielded diphenyl.

Experimental.

(All m. p.s are uncorrected.)

2-Benzylcyclopentanol.—2-Benzylidene*cyclo*pentanone was prepared in the analogous way to that described by Vorländer and Kunze (*Ber.*, 1926, **59**, 2081) for 2-benzylidene*cyclo*hexanone. It was hydrogenated quantitatively to 2-benzyl*cyclo*pentanol, b. p. 145—146°/15 mm., in glacial acetic acid with Adams's catalyst at 7 atmospheres and room temperature.

Benzoylcyclopentane.—*cyclo*Pentanecarboxyl chloride (3·3 g.) (Haworth and Perkin, *J.*, 1894, **65**, 99) in dry benzene (30 ml.) was added to anhydrous aluminium chloride (3·3 g.) in benzene (60 ml.), and the mixture warmed on the water-bath for 1 hour after evolution of hydrogen chloride had ceased. The mixture was then cooled and decomposed with ice and dilute hydrochloric acid. The benzene layer was washed with dilute sodium hydroxide solution, dried (Na_2SO_4), and distilled, giving the *ketone* (3·3 g.) as a colourless oil, b. p. 156—160°/15 mm. (Found: C, 82·6; H, 8·5. $C_{12}H_{14}O$ requires C, 82·75; H, 8·05%). The *semicarbazone* separated from benzene–light petroleum (b. p. 60—80°) as colourless prisms, m. p. 96—97° (Found: C, 67·3; H, 7·35. $C_{13}H_{17}ON_3$ requires C, 67·5; H, 7·35%). The 2 : 4-*dinitrophenylhydrazone* separated from glacial acetic acid as large yellow needles, m. p. 142—143° (Found: C, 61·25; H, 5·2. $C_{18}H_{18}O_4N_4$ requires C, 61·0; H, 5·1%).

α-Hydroxybenzylcyclopentane.—A solution of potassium (4·8 g.) in an excess of absolute ethano was heated on the water-bath under reduced pressure until only a trace of ethanol remained. Benzoylcyclopentane (6·0 g.) in dry ether (48 ml.) was added, the mixture heated under reflux for 18 hours, cooled, and acidified (dilute hydrochloric acid), and the ethereal layer separated, washed with water, dried (Na_2SO_4), and distilled, giving a colourless alcohol (4·6 g.), b. p. 122°/3 mm. (Found: C, 81·8; H, 9·1. Calc. for $C_{12}H_{16}O$: C, 81·8; H, 9·1%).

Dehydrations with Phosphoric Oxide.—The carbinol (1·0 g.) and phosphoric oxide (2·0 g.) were heated at 120° (oil-bath) for 30 minutes. The temperature of the bath was then raised to 150°, the olefin distilling directly, under reduced pressure, as a colourless mobile oil (0·7 g.), b. p. 109—111°/12 mm. In all cases the product contained no active hydrogen, decolorised bromine in carbon tetrachloride, and absorbed one mol. of hydrogen at room temperature and atmospheric pressure in presence of Adams's catalyst.

The olefin from 1-benzylcyclopentanol had light absorption in hexane: $\lambda_{max.}$ 2473 A.; $\log \varepsilon_{max.} = 3{\cdot}18$; $\lambda_{min.}$ 2320 A.; $\log \varepsilon_{min.} = 3{\cdot}05$.

The olefin from α-hydroxybenzylcyclopentane had light absorption in ethanol: $\lambda_{max.}$ 2466 A.; $\log \varepsilon_{max.} = 3{\cdot}26$; $\lambda_{min.}$ 2297 A.; $\log \varepsilon_{min.} = 2{\cdot}78$.

Dehydrations with Anhydrous Oxalic Acid.—Equal weights of the carbinol and oxalic acid were heated on the water-bath for 3 hours. Water was then added, the mixture extracted with ether, and the extract washed with sodium carbonate solution, dried (Na_2SO_4), and distilled.

1-Benzylcyclopentanol (1·25 g.) gave the olefin (0·7 g.), b. p. 115°/14 mm., as a colourless mobile oil.

α-Hydroxybenzylcyclopentane (3·0 g.) gave a colourless oil (1·0 g.), b. p. 120—125°/15 mm. (the required olefin) (Light absorption in ethanol: $\lambda_{max.}$ 2485 A.; $\log \varepsilon_{max.} = 3{\cdot}71$; $\lambda_{min.}$ 2280 A.; $\log \varepsilon_{min.} = 3{\cdot}36$), and a pale yellow oil of unknown constitution (0·8 g.), b. p. 220°/15 mm. (Found: C, 85·3; H, 8·8%).

Cyclisation of the Olefins.—The procedure followed was the same in all cases. The olefin (1·0 g.), in dry carbon disulphide (5 ml.), was added during several hours to anhydrous aluminium chloride (1·7 g.) in carbon disulphide (35 ml.) at 0°. The mixture was kept at 0° for 48 hours, and the clear liquid was decanted and decomposed with ice and dilute hydrochloric acid. The organic layer was separated, dried ($CaCl_2$), and fractionated, affording 1 : 3-*endo*ethylene-1 : 2 : 3 : 4-tetrahydronaphthalene (II) (0·4 g.), b. p. 115°/15 mm., as a colourless oil from all the olefins except that obtained by oxalic acid dehydration of α-hydroxybenzylcyclopentane. In this case, the olefin (1·5 g.) yielded on cyclisation a saturated, unidentified colourless oil (0·3 g.), b. p. 120—125°/15 mm.

Nitration of the Product obtained by Cyclisation of the Olefin formed on Phosphoric Oxide Dehydration of 1-Benzylcyclopentanol.—The saturated hydrocarbon, which consisted mainly of (II), was nitrated in the cold for 2 hours with concentrated sulphuric acid–concentrated nitric acid (3 : 2 by vol.). The *dinitro*-compound precipitated by water solidified on trituration with light petroleum and gave colourless needles, m. p. 154°, from methanol (Found: C, 57·75; H, 4·5. $C_{12}H_{12}O_4N_2$ requires C, 58·05; H, 4·8%). The yields varied from 10 to 20%. The light-petroleum mother-liquors contained the main product of the reaction, a brown oil having a pronounced ketonic odour.

Chromic Acid Oxidation of the Products from the Cyclisations.—The hydrocarbon (0·5 g.), sodium dichromate (1·0 g.), and acetic acid (5·5 ml.) were heated under reflux for 2½ hours. *iso*Propyl alcohol was added to remove the excess of chromic acid, the solvents were removed at 50° (reduced pressure), the residue was extracted with ether, and the extracts were washed with sodium carbonate solution, dried (Na_2SO_4), and distilled. 1 : 3-*endo*Ethylene-1 : 2 : 3 : 4-tetrahydro-4-ketonaphthalene (0·3 g.), b. p. 165°/20 mm., was obtained from the hydrocarbons formed in phosphoric oxide experiments, and in lower yield (0·08 g.) from the hydrocarbon formed by cyclisation of the olefin from oxalic acid dehydration of 1-benzylcyclopentanol (in this case, 0·2 g. of original material was recovered).

The semicarbazone of the ketone separated as colourless needles (from dilute methanol), m. p. 190—191° (after liquefaction and resolidification at 170—171° owing to loss of methanol of crystallisation), not depressed on admixture with an authentic specimen. The 2 : 4-dinitrophenylhydrazone formed dark red needles (from glacial acetic acid), m. p. 245—246° (decomp.), not depressed on admixture with an authentic specimen.

On oxidation of the cyclised product from the olefin formed by oxalic acid dehydration of α-hydroxybenzylcyclopentane, the original material was recovered apparently unchanged, as no 2 : 4-dinitrophenylhydrazone could be isolated from the product.

Catalytic Dehydrogenation of 1 : 3-endo*Ethylene-1 : 2 : 3 : 4-tetrahydronaphthalene.*—The hydrocarbon (0·5 g.) was heated under reflux (bath-temp. 255°) for 3 hours with palladium black (0·15 g.). Approx. 1 mol. of hydrogen was liberated. The mixture solidified to a colourless mass of crystals, m. p. 35—37°, which appeared to contain diphenyl. This was confirmed by preparation of the 4 : 4′-dinitro-derivative, colourless needles (from methanol), m. p. 236°, not depressed on admixture with an authentic specimen (Found: C, 58·4; H, 3·45. Calc. for $C_{12}H_8O_4N_2$: C, 58·3; H, 3·3%).

Thanks are offered to the Department of Scientific and Industrial Research for a maintenance grant (to L. H. G.), to Professor Wilson Baker, F.R.S., for specimens of the semicarbazone and 2 : 4-dinitrophenylhydrazone of 1 : 3-*endo*ethylene-1 : 2 : 3 : 4-tetrahydro-4-ketonaphthalene, and to Professor G. R. Clemo, F.R.S., for his interest.

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NEWCASTLE-ON-TYNE, 1.

[*Received, October 21st,* 1950.]

195. *Eburicoic Acid.*

By F. N. Lahey and P. H. A. Strasser.

Eburicoic acid, isolated as its acetyl derivative from the naturally grown fungus, *Polyporus anthracophilus* Cooke, is shown to be a tetracyclic hydroxy-acid of the triterpene series, of formula $C_{30}H_{48}O_3$ and not $C_{27}H_{44}O_3$ as suggested by Gascoigne, Holker, Ralph, and Robertson (*Nature*, 1950, **166**, 652). It contains one reactive and one inert ethylenic linkage, and the presence of the system $\cdot CH_2 \cdot C{:}C \cdot CH_2 \cdot$ has been established by oxidation to the chromophore $\cdot CO \cdot C{:}C \cdot CO$ recognised by its characteristic absorption spectrum.

By conversion of the carboxyl group into a methyl group a new triterpene alcohol, eburicol, has been prepared.

The report by Gascoigne, Holker, Ralph, and Robertson (*Nature*, 1950, **166**, 652) of the occurrence of eburicoic acid in the fungus *Polyporus anthracophilus* Cooke makes it desirable to publish our results on this acid obtained from the same source. Mr. J. L. Somerville, Australian Newsprint Mills, Boyer, Tasmania, observed several years ago that the " white rot " in a sample of decayed *Eucalyptus regnans*, on extraction with alcohol, yielded a crystalline acid, and he very kindly made this acid and supplies of the fungus available to us for further investigation. We have isolated from the mycelium of the fungus, in yields of up to 70%, the acetyl derivative of a monobasic acid recorded by Gascoigne *et al.* We were unaware of the identity of this acid with eburicoic acid which now appears to have been established by the Liverpool workers. We accept this identification and adopt the name given to the acid by the earlier workers, Kariyone and Kuruno (*J. Pharm. Soc. Japan*, 1940, **60**, 110, 318).

On the basis of analytical figures obtained for eburicoic acid and four of its derivatives, Gascoigne *et al.* put forward a formula $C_{27}H_{44}O_3$ for the acid. However, the present communication describes twenty-seven derivatives and degradation products, analyses of which clearly indicate the formula $C_{30}H_{48}O_3$ originally suggested by Kariyone and Kuruno; but for consistent analyses figures we found it necessary to sublime the free acid under a high vacuum.

Hydrolysis of the acetate gave the free acid, m. p. 292—293°, $[\alpha]_D^{17}$ +34° (in pyridine), in good agreement with the values given by Gascoigne *et al.* [m. p. 293°, $[\alpha]_D^{17}$ +35·6° (in pyridine)]. Three of the four derivatives recorded by these workers have also been prepared by us and there is reasonable agreement between our results (see Experimental).

Eburicoic acid is a weak acid which can be titrated with standard alkali in alcohol solution. Its methyl ester, readily prepared by the action of diazomethane, is very stable towards alkali, indicating that the carboxyl group is attached to a tertiary carbon atom. Benzoylation of the methyl ester proceeded readily, but benzoyleburicoic acid resisted methylation by diazomethane in ether although it took place slowly in acetone. This suggests that the carboxyl and the hydroxyl group are close together, resistance to methylation being caused by steric hindrance by the large benzoyl group.

Eburicoic acid and its simple derivatives gave a yellow colour with tetranitromethane in chloroform and positive tests in the Liebermann–Burchard and Salkowski reactions. Thus we concluded that eburicoic acid is a monohydroxy-carboxylic acid, $C_{30}H_{48}O_3$, of the triterpene series, and thus isomeric with a number of well-defined acids of this class.

Eburicoic acid on mild oxidation with chromic acid yielded a ketonic acid, eburiconic acid, $C_{30}H_{46}O_3$, m. p. 232° (semicarbazone, m. p. 223°). The alcoholic group present in eburicoic acid is thus secondary, and probably at position 2 in the triterpene nucleus in common with most of the triterpenes of known structure, although proof of this has not yet been obtained.

Reduction of methyl acetyleburicoate, m. p. 157—158°, with hydrogen at high temperature and pressure in the presence of Raney nickel yielded an unsaturated (tetranitromethane) product, m. p. 157—158°, which did not depress the melting point of the starting material. The product was, however, methyl acetyldihydroeburicoate, also produced by quantitative hydrogenation at atmospheric temperature and pressure in the presence of Adams's catalyst in which one mole of hydrogen was absorbed. Furthermore, methyl acetyleburicoate absorbed two atoms of oxygen per molecule from perbenzoic acid, indicating the presence of two ethylenic linkages, and methyl acetyldihydroeburicoate absorbed only one.

From the reaction of perbenzoic acid on methyl acetyleburicoate an "oxide," m. p. 208°, of probable formula $C_{33}H_{52}O_4$ was isolated which gave no colour with tetranitromethane. On

the other hand, the product of the same reaction on methyl acetyldihydroeburicoate had the composition, $C_{33}H_{52}O_4$, and is thus isomeric with methyl acetyleburicoate; this product gave an intense yellow colour with tetranitromethane, and its ultra-violet absorption spectrum, (maxima at 243 and 251 mμ.) points to the presence of two conjugated double bonds, the formation of which can readily be explained by loss of water from an unstable oxide intermediate. Birchenough and McGhie (*J.*, 1949, 2038) have shown that perbenzoic acid reacted with α-dihydrolanosteryl acetate to give a labile intermediate " oxide " which readily passed into a diene during recrystallisation. The $\lambda_{max.}$ values of the absorption spectrum of α-dihydroagnosteryl acetate thus formed are identical with those of our product which we have termed methyl acetyl*iso*eburicoate.

From the evidence so far considered we conclude that eburicoic acid is a tetracyclic triterpene acid and that since it has no characteristic ultra-violet absorption spectrum the two double bonds present are not conjugated. Other tetracyclic acids to which eburicoic acid may bear some relation are polyporenic acid A (Cross and Jones *J.*, 1940, 1491) and the elemadienolic acids (α- and β-elemolic acids) (Ruzicka, Rey, Spillmann, and Baumgartner, *Helv. Chim. Acta*, 1943, **26**, 1638). Further reactions were carried out in an endeavour to establish such a relationship.

With ozone methyl acetyleburicoate yielded 0·5 mole of formaldehyde, indicating an exocyclic methylene group. This double bond is that which is readily reduced, as methyl acetyldihydroeburicoate gave no formaldehyde on ozonolysis. These results are in close agreement with those obtained by Cross and Jones (*loc. cit.*) with polyporenic acid A. The non-volatile product from the ozonolysis of methyl acetyleburicoate was a ketonic methyl ester acetate, $C_{33}H_{50}O_5$.

Oxidation of dihydroeburicoic acid with chromic acid at 40° gave dihydroeburiconic acid, but methyl acetyldihydroeburicoate gave a product, $C_{33}H_{50}O_6$, as bright yellow prisms having an intense absorption maximum at 270—272 mμ. The replacement of four hydrogen atoms by two oxygen atoms and the light absorption indicated the chromophore ·CO·C:C·CO, formed by oxidation of ·CH_2·C:C·CH_2, so the product must be methyl acetyldihydrodiketoeburicoate. This arrangement of two ketone groups with a conjugated double bond between them has been established for other yellow compounds formed in the triterpene series (*Helv. Chim. Acta*, 1942, **25**, 1394, 1405; *Annalen*, 1939, **539**, 219; *J.*, 1950, 1562). As well as supplying valuable structural evidence this oxidation confirms the presence of the second, the inert, double bond which had previously been indicated by perbenzoic acid titration.

The oxidation of methyl acetyleburicoate with chromic acid at 70° gave a mixture, from which two well-defined yellow crystalline solids were readily separated by chromatography. For one, $C_{33}H_{48}O_6$, yellow prisms, m. p. 143—145°, the absorption spectrum with a maximum at 264—267 mμ. again indicated the presence of the chromophore ·CO·C:C·CO. The main product, $C_{33}H_{46}O_7$, crystallised in yellow needles, m. p. 195° ($\lambda_{max.}$ 268—270 mμ.); in the formation of this compound oxidation has taken place also at the reactive double bond with the elimination of the methylene group, forming a new keto-group not in close proximity to the main chromophore; the product is therefore a methyl triketo-ester acetate.

The possibility existed that the alcohol resulting from the conversion of the carboxyl group of eburicoic acid into a methyl group might be identical with one of the well-defined tetracyclic alcohols. This conversion was attempted by the standard procedure. Thionyl chloride reacted with acetyleburicoic acid to form an acid chloride, but hydrogen chloride was added at the double bond, forming a compound $C_{33}H_{50}O_3Cl_2$; but use of oxalyl chloride gave a compound, in poor yield, which was probably the required acid chloride. We found, however, that the conversion of the carboxyl group into the aldehyde group could be accomplished readily by another route. Lithium aluminium hydride converted either methyl eburicoate or methyl acetyleburicoate into a new crystalline diol containing one secondary and one primary hydroxyl group. Its diacetate on careful hydrolysis was converted into the monoacetate, having a free primary alcohol group which was then oxidised to the corresponding aldehyde. Wolff–Kishner reduction then yielded eburicol $C_{30}H_{50}O$, m. p. 158—159°, $[\alpha]_D^{17}$ +66°, isomeric but not identical with any known triterpene alcohol. Catalytic reduction of its acetate gave dihydroeburicyl acetate, which on hydrolysis gave dihydroeburicol. These are not identical with dihydro-β-tritelemol and its acetate (Ruzicka and Häusermann, *Helv. Chim. Acta*, 1942, **25**, 439) formed by a similar conversion from dihydro-β-elemolic acid. Like polyporenic acid A (Cross and Jones, *loc. cit.*), eburicoic acid is not readily isomerised. Other points of similarity with polyporenic acid A have been established in this paper and this acid may perhaps be a hydroxy-eburicoic acid.

Experimental.

All m. p.s are corrected. Rotations were measured in chloroform solution unless otherwise stated.

Extraction of the Fungus.—Dried mycelium of *Polyporus anthracophilus* Cooke (150 g.) was refluxed with alcohol (*ca.* 1 l.) for 10 minutes and filtered hot with suction. The residue was extracted twice more with smaller volumes of alcohol. The combined alcoholic extracts deposited the crude triterpene on storage. By filtration and concentration, several crops of crystalline material were obtained, of unchanged physical properties. The yield of crude triterpene thus obtained varied from 58 to 70% of the weight of fungus. It was recrystallised three times from alcohol, then twice from glacial acetic acid, and finally from alcohol. After being dried in a vacuum at 140° for 12 hours acetyleburicoic acid melted at 259° and had $[\alpha]_D^{16}$ +42° (*c*, 0·42) (Found: C, 76·8; H, 9·8. Calc. for $C_{33}H_{50}O_4$: C, 77·1; H, 10·0%). Gascoigne *et al.* report m. p. 256—257°, $[\alpha]_D^{20}$ +35·8°.

Eburicoic Acid.—Acetyleburicoic acid was heated with aqueous-alcoholic potassium hydroxide at 40° for 24 hours and worked up in the usual way. Crystallisation three times from alcohol and finally from chloroform–ethanol gave minute needles of *eburicoic acid*, m. p. 292—293°, $[\alpha]_D^{17}$ +34° (*c*, 1·2 in pyridine), +50° (*c*, 0·25 in chloroform) [Found: C, 78·5; H, 10·5%; equiv., 458 (cholic acid used for standardisation). Calc. for $C_{30}H_{48}O_3$: C, 78·9; H, 10·6%; equiv., 456]. The Liebermann–Burchard test gave an intense red colour and the Salkowski test an orange-red colour.

Methyl eburicoate. Eburicoic acid was methylated with diazomethane in ether, and the product crystallised three times from methanol from which it separated as white needles, m. p. 127—129°. After being dried in a vacuum at 80° for 4 hours it had m. p. 142—145°. Recrystallisation from ethyl acetate then gave the ester, m. p. 146—147°, $[\alpha]_D^{18}$ +45° (*c*, 1·83) (Found: C, 79·1; H, 10·4; OMe, 6·6. Calc. for $C_{31}H_{52}O_3$: C, 79·2; H, 10·6; OMe, 6·6%). The sample for analysis was sublimed in a high vacuum. Attempted hydrolysis of methyl eburicoate with N-alcoholic alkali yielded unchanged material. With tetranitromethane in chloroform it gave a deep yellow colour. Gascoigne *et al.* report m. p. 140—141°.

Methyl acetyleburicoate. This was prepared either by methylation of acetyleburicoic acid with diazomethane in ether or by acetylation of methyl eburicoate with acetic anhydride and pyridine, and was isolated in the usual way. After three crystallisations from methanol the methyl ester separated in long, slender, glistening needles which, after being dried in a vacuum at 120° for 24 hours, had m. p. 157—158°, $[\alpha]_D^{18}$ +48° (*c*, 0·52) (Found: C, 77·4; H, 10·3; OMe, 5·9%. Calc. for $C_{33}H_{54}O_4$: C, 77·3; H, 10·2; OMe 6·1%). Gascoigne *et al.* report m. p. 153—154°.

Benzoyleburicoic acid. Eburicoic acid and benzoyl chloride in pyridine were kept at room temperature for 24 hours. The product, crystallised twice from acetone, gave *benzoyleburicoic acid* in squat prisms, m. p. 166°, $[\alpha]_D^{18}$ +57° (*c*, 0·912) (Found: C, 79·8; H, 9·1. $C_{37}H_{54}O_4$ requires C, 79·3; H, 9·3%).

Attempts to methylate this with diazomethane in ether yielded unchanged starting material. When benzoyleburicoic acid in acetone was treated with excess of diazomethane in ether and kept for 48 hours at 0° *methyl benzoyleburicoate* was formed, which after crystallisation from acetone formed needles, m. p. 200—201°, $[\alpha]_D^{18}$ +71° (*c*, 0·418). For analysis a sample was dried in a vacuum at 140° for 8 hours (Found: C, 79·7; H, 9·2; OMe, 5·5. $C_{38}H_{54}O_4$ requires C, 79·4; H, 9·4; OMe, 5·4%). The same product was obtained by benzoylating methyl eburicoate.

Eburiconic Acid.—Tetraeburicoic acid (1·22 g.) in purified glacial acetic acid (60 ml.) at 40° was added chromic acid in acetic acid (12 ml. of N.) during 1 hour. Next morning the solution was treated with a few drops of methanol to destroy excess of chromic acid and then poured into water (400 ml.). The product was filtered off, washed with water, and crystallised twice from acetone. *Eburiconic acid* separated in fine white needles, m. p. 232°, $[\alpha]_D^{20}$ +49° (*c*, 0·512) (Found: C, 79·1; H, 10·2. $C_{30}H_{46}O_3$ requires C, 79·3; H, 10·1%).

The semicarbazone, formed in the normal way, melted at 223° (Found: C, 72·8; H. 9·8. $C_{31}H_{49}O_3N_3$ requires C, 72·8; H, 9·6%).

Methyl Acetyldihydroeburicoate.—Methyl acetyleburicoate (1 g.) in methanol (100 ml.) was reduced with hydrogen in the presence of Raney nickel at 100°/100 atm. for 2 hours. The filtered solution was concentrated, yielding *methyl acetyldihydroeburicoate*, needles, m. p. 157—158°, $[\alpha]_D^{18}$ +56° (*c*, 2·8) (Found: C, 76·9; H, 10·7. $C_{33}H_{54}O_4$ requires C, 77·0; H, 10·5%), which gave a distinct yellow colour with tetranitromethane. The same reduction was effected with Adams's platinum catalyst in ethanol at atmospheric pressure: reduction ceased after the uptake of one mole of hydrogen.

Methyl acetyldihydroeburicoate (100 mg.) was dissolved in ethanol (20 ml.) to which was added 2 ml. of N-potassium hydroxide, and the solution kept overnight. The product isolated by dilution with water and filtration was crystallised from chloroform–methanol, yielding *methyl dihydroeburicoate*, m. p. 135—136°, $[\alpha]_D^{20}$ +44° (*c*, 1·1) (Found: C, 78·5; H, 11·2. $C_{31}H_{52}O_3$ requires C, 78·8; H, 11·0%).

Acetyldihydroeburicoic Acid.—Catalytic reduction of acetyleburicoic acid (1 g.) in ethanol (100 ml.) with Raney nickel at 100°/100 atm. yielded this *acid*, which crystallised from methanol in fine small needles, m. p. 268—270°, $[\alpha]_D^{20}$ +47° (*c*, 1·384) (Found: C, 76·5; H, 10·5. $C_{32}H_{52}O_4$ requires C, 76·8; H, 10·4%). Hydrolysis of a sample with aqueous-alcoholic alkali gave *dihydroeburicoic acid* in fine needles (after crystallisation from chloroform–methanol), m. p. 286—288°, $[\alpha]_D^{17}$ +55° (*c*, 0·22) (Found: C, 78·3; H, 11·1. $C_{30}H_{50}O_3$ requires C, 78·6; H, 10·9%).

Titrations with Perbenzoic Acid.—To a solution of methyl acetyleburicoate (1 g.) in chloroform at 0°, a 200% excess of perbenzoic acid in chloroform was added and the mixture kept at 0°. Aliquot portions were withdrawn at intervals and treated with excess of potassium iodide, the solutions acidified with acetic acid, and the iodine was titrated with 0·1N-sodium thiosulphate. After 24 hours 2 atoms

of oxygen per molecule were absorbed and no further reaction took place. The bulk of the solution was then treated with excess of potassium iodide and sodium thiosulphate with shaking, and the chloroform layer separated, washed with sodium carbonate solution and water, then dried, and distilled. The residue was crystallised twice from methanol, giving the "*oxide*," long white needles, m. p. 208°, $[\alpha]_D^{17}$ +4° (*c*, 2·416) (Found: C, 73·3; H, 9·5. $C_{32}H_{52}O_6$ requires C, 72·8; H, 9·6%). The product gave no colour with tetranitromethane in chloroform.

Methyl acetyldihydroeburicoate on perbenzoic acid titration as above absorbed 1 atom of oxygen per molecule after 24 hours; reaction then ceased. Working up the product in the usual way gave *methyl acetyliso*eburicoate, m. p. 167°, $[\alpha]_D^{20}$ +59° (*c*, 0·8) (Found: C, 77·2; H, 10·2. $C_{33}H_{52}O_4$ requires C, 77·3; H, 10·1%), $\lambda_{max.}$ 243 and 251 mμ., $\varepsilon_{max.}$ 17,300 and 11,700. With tetranitromethane in chloroform it gave a bright yellow colour.

Ozonolysis of Methyl Acetyleburicoate.—Methyl acetyleburicoate (1 g.) in glacial acetic acid (80 ml.) was treated with ozone and oxygen for 1 hour. The solution was then diluted with 1 l. of water and distilled. The distillate (approx. 800 ml.), when treated with 2:4-dinitrophenylhydrazine hydrochloride, gave formaldehyde 2:4-dinitrophenylhydrazone, m. p. 167° undepressed on admixture with an authentic sample. The yield was 0·2 g. (50%). The residue from the distillation was extracted with ether, the ethereal solution dried and distilled, and the residue crystallised twice from methanol. The *product* separated in needles, m. p. 181—183°, $[\alpha]_D^{18}$ +51° (*c*, 1·48) (Found: C, 74·9; H, 10·1. $C_{32}H_{50}O_5$ requires C, 74·7; H, 9·7%).

Dihydroeburiconic Acid.—Dihydroeburicoic acid (100 mg.) was oxidised with chromic acid, as in the preparation of eburiconic acid above, yielding *dihydroeburiconic acid* as leaflets, m. p. 240—243°, $[\alpha]_D$ +50° (*c*, 0·3) (Found: C, 78·6; H, 10·8. $C_{30}H_{44}O_5$ requires C, 78·9; H, 10·6%).

Methyl Acetyldihydrodiketoeburicoate.—A solution of methyl acetyldihydroeburicoate (0·6 g.) in acetic acid (50 ml.), kept at 70°, was treated during 1 hour with chromic acid (0·7 g.) in acetic acid (10 ml.). The solution was then set aside overnight, whereafter methanol was added to destroy excess of chromic acid, and the whole poured into water and extracted thoroughly with ether. The ethereal extract was washed with sodium carbonate solution, then water, and dried (Na_2SO_4). The residue after removal of the ether was crystallised from methanol and the *methyl acetyldihydrodiketoeburicoate* after two more crystallisations from the same solvent was obtained as large yellow prisms, m. p. 174°, $[\alpha]_D^{17}$ +81° (*c*, 0·34) (Found: C, 73·0; H, 9·4. $C_{32}H_{50}O_6$ requires C, 73·1; H, 9·2%), $\lambda_{max.}$ (in alcohol) 270—272 mμ.; $\varepsilon_{max.}$ 7500.

Oxidation of Methyl Acetyleburicoate.—This ester (4 g.) in acetic acid (300 ml.) was oxidised by the dropwise addition of chromic acid (5 g.) in acetic acid at 70°. The mixture was kept overnight and worked up as in the preceding experiment. The crude product was a yellow resinous mass which failed to crystallise. It was dissolved in light petroleum–benzene (1:1) (50 ml.) and filtered through neutralised alumina (80 g.). Light petroleum–benzene (1:1) removed *methyl acetyldiketoeburicoate* (50 mg.) which after several recrystallisations from methanol and acetone formed bright yellow prisms, m. p. 143—145°, $[\alpha]_D^{18}$ +70° (*c*, 0·9) (Found: C, 73·2; H, 9·0. $C_{33}H_{48}O_6$ requires C, 73·3; H, 8·9%), $\lambda_{max.}$ (in alcohol) 264—267 mμ.; ε 6900. Benzene or benzene–ether (3:1) removed a second yellow *constituent* (2·1 g.) which after four crystallisations from methanol separated as fine yellow needles, m. p. 195°, $[\alpha]_D^{18}$ +67° (*c*, 1·04), $\lambda_{max.}$ (in alcohol) 268—270 mμ.; ε = 7900. For analyses a sample was sublimed in a high vacuum (Found: C, 71·0; H, 8·4. $C_{32}H_{46}O_7$ requires C, 70·9; H, 8·5%).

Acid Chloride Formation.—Acetyleburicoic acid (1·5 g.) was treated with thionyl chloride (15 ml.) at room temperature. The mixture was kept for 3 hours, excess of thionyl chloride removed in a vacuum, and the residue kept in a vacuum-desiccator over solid sodium hydroxide for 48 hours. The *product* crystallised from *n*-hexane in white needles, m. p. 193—195° (Found: C, 69·6; H, 9·1; Cl, 12·6. $C_{32}H_{50}O_3Cl_2$ requires C, 69·6; H, 9·0; Cl, 12·8%).

When acetyleburicoic acid (2 g.) was heated under reflux with oxalyl chloride (5 ml.) for 4 hours and the excess of oxalyl chloride removed under reduced pressure a product was obtained which dissolved readily in *n*-hexane and from this a small amount of crystalline material of rather indefinite m. p. separated which was thought to be the desired acid chloride. It was not analysed or used further.

Eburicodiol.—A suspension of lithium aluminium hydride (0·5 g.) in dry ether (20 ml.) was gently boiled under nitrogen for 15 minutes, then ground, and further heated for 5 minutes. Methyl eburicoate (1·6 g.) in ether (50 ml.) was then run in during 15 minutes. The mixture was set aside for 30 minutes and then treated with sodium hydroxide solution, followed by excess of dilute hydrochloric acid. The ethereal layer was separated, washed with water, dried, and concentrated to 20 ml. Small clusters of needles separated which, after crystallisation from alcohol or acetone, gave *eburicodiol*, m. p. 212—213°, $[\alpha]_D^{17}$ +55° (*c*, 1) (Found: C, 80·9; H, 11·4. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·3%). The same product was obtained from methyl acetyleburicoate. Attempts to form an *iso*propylidene derivative failed.

Acetylation with acetic anhydride–pyridine gave the *diacetate* in fine needles, m. p. 134° after crystallisation from methanol and drying in a vacuum at 100° for 24 hours. Unless thus dried, the product melted at 115°, resolidified, and remelted at 134°. It had $[\alpha]_D^{17}$ +45° (*c*, 1) (Found: C, 77·3; H, 10·2. $C_{34}H_{54}O_4$ requires C, 77·6; H, 10·3%).

To the diacetate (2 g.) in alcohol (70 ml.) and water (3 ml.) was added 0·023N-KOH (190 ml.). The resulting solution was refluxed for 2 hours and worked up in the usual way. The product was dissolved in benzene–light petroleum (b. p. 40—60°) and filtered through neutralised alumina (40 g.). Benzene eluted the main product, *eburicodiol 2-acetate*, which after three crystallisations from chloroform–methanol formed small white needles, m. p. 166—167°, $[\alpha]_D^{17}$ +56° (*c*, 1) (Found: C, 79·3; H, 10·8. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·7%).

Eburicalyl Acetate.—To the above monoacetate (0·666 g.) in acetic acid (100 ml.) and ether (350 ml.) was added chromic acid (150 mg.) in acetic acid (4·8 ml.) during 1 hour. The whole was set aside for 2 hours, then diluted largely with water, and the ethereal layer separated. The aqueous layer was further extracted with ether, and the extracts were combined, washed with sodium carbonate solution and water, and dried. After removal of the ether, the residue, dissolved in light petroleum (b. p. 40—60°), was filtered through neutralised alumina. Benzene–light petroleum (1 : 1) eluted *eburicalyl acetate* which after three crystallisations from methanol melted over the range 140—144°. It had $[\alpha]_D^{17}$ +53° (*c*, 0·42) (Found: C, 79·1; H, 10·6. $C_{33}H_{56}O_3$ requires C, 79·7; H, 10·4%).

Eburicyl Acetate.—The above aldehyde (100 mg.), sodium ethoxide (from Na, 1·5 g., and alcohol, 15 ml.), and hydrazine hydrate (100%; 2·5 ml.) were heated at 200° for 17 hours. The crude product, isolated in the usual way, was acetylated with acetic anhydride–pyridine and the product, in light petroleum (b. p. 40—60°), filtered through neutralised alumina. Light petroleum–benzene (9 : 1) eluted *eburicyl acetate* (40 mg.) which crystallised from methanol in plates, m. p. 138—139°, $[\alpha]_D^{17}$ +66° (*c*, 0·25) (Found: C, 82·2; H, 11·4. $C_{33}H_{52}O_3$ requires C, 82·1; H, 11·1%).

Hydrolysis of this acetate yielded *eburicol*, m. p. 158—159°, $[\alpha]_D^{17}$ +66° (*c*, 0·3) (Found: C, 84·6; H, 11·9. $C_{31}H_{52}O$ requires C, 84·5; H, 11·7%).

Eburicyl acetate (20 mg.), hydrogenated in alcohol solution with hydrogen in the presence of Adams's catalyst, yielded *dihydroeburicyl acetate* which crystallised from methanol in flat needles, m. p. 127°, $[\alpha]_D^{17}$ +79° (*c*, 0·22) (Found: C, 81·7; H, 11·7. $C_{33}H_{54}O_3$ requires C, 81·7; H, 11·5%). Hydrolysis of this gave *dihydroeburicol*, leaflets (from methanol), m. p. 164—165°, $[\alpha]_D^{20}$ +40° (*c*, 0·2) (Found: C, 83·8; H, 12·4. $C_{31}H_{52}O$ requires C, 84·1; H, 12·2%).

The authors thank Mr. J. L. Somerville for the supply of fungus material for this investigation, Dr. D. H. R. Barton for very helpful discussions and suggestions, and Dr. A. J. Birch for valued criticisms. Part of the work was carried out at Cambridge during the tenure of a Nuffield Research Fellowship held by one of the authors (F. N. L.) who is grateful to Professor A. R. Todd, F.R.S., for the hospitality of his laboratory. A research grant from the Chemical Society is gratefully acknowledged.

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[*Received, October* 31*st*, 1950.]

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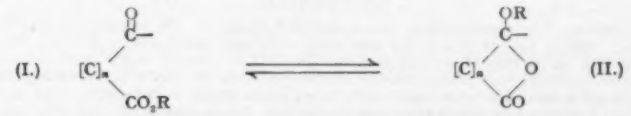
196. *Infra-red Spectroscopy and Structural Chemistry. Part I. Keto–Lactol Tautomerism.*

By JOHN FREDERICK GROVE and H. A. WILLIS.

The application of infra-red spectroscopy to the study of keto–lactol tautomerism is discussed, and a method is described whereby the lactol and the open-chain form of aldehydic and ketonic acids may be recognised. The normal and the *pseudo*-esters of γ-aldehydic and -ketonic acids are readily distinguished by the frequencies of the stretching vibrations of the C=O groups. The methods have been tested with some simple acids and esters of known structure and applied to other molecules of unknown structural configuration.

NUMEROUS examples of keto–lactol tautomerism have been described in the literature, and many of the substances which have been shown to exhibit this phenomenon fall into the class of γ-aldehydic and ketonic acids (I; $n = 2$).



Such compounds, which may be recognised by the formation of neutral monoacetyl derivatives (II; R = Ac) derived from the lactol form (II; R = H), may give rise to two series of esters, the normal carboxylic esters (I) and the hydroxy-lactonic or *pseudo*-esters (II). Keto–lactol tautomerism is shown by a number of substances possessing biological activity, such as *o*-benzoylbenzoic acid (Sexton and Templeman, *Nature*, 1948, **161**, 974) and the weakly antibacterial mould products, penicillic acid (Birkinshaw, Oxford, and Raistrick, *Biochem. J.*, 1936, **30**, 394; and Raphael, *Nature*, 1947, **160**, 261; *J.*, 1947, 805) and gladiolic acid (Brian, Curtis, Grove, Hemming, and McGowan, *Nature*, 1946, **157**, 697; Grove, unpublished results), and it was our interest in the latter compound which led us to examine the known methods of studying this phenomenon and of distinguishing between normal and *pseudo*-esters.

The normal esters of aldehydic acids retain the characteristic chemical reactions of the aldehyde group and these may be used for the purpose of identification. Newman and McCleary (*J. Amer. Chem. Soc.*, 1941, **63**, 1537) have reviewed some of the methods for the allocation of structures to the esters of keto-acids. Chemical reactions, and in particular the hydrolysis of *pseudo*-esters by concentrated sulphuric acid to give highly coloured solutions, are stated to be unreliable for the assignment of structure, as also are such physical properties as melting point and solubility. Among other physical methods which have been used, the determination of molecular refractivity has proved of value for liquid esters (Egerer and Meyer, *Monatsh.*, 1913, **34**, 69; Auwers and Heinze, *Ber.*, 1919, **52**, 584; Lutz, Merrit, and Couper, *J. Org. Chem.*, 1939, **4**, 95). The polarographic method described by Wawzonek *et al.* (*J. Amer. Chem. Soc.*, 1944, **66**, 827) does not always give a satisfactory differentiation (Schmid, Hochweber, and von Halban, *Helv. Chim. Acta*, 1948, **31**, 354).

Ultra-violet absorption spectroscopy has been used with success in the study of keto-lactol tautomerism in the aromatic acids, phthalonic acid (Buu-Hoï and Lin, *Compt. rend.*, 1939, **209**, 346), *o*-formylbenzoic acid (Buu-Hoï, *Compt. rend.*, 1939, **209**, 221), opianic acid and substitued opianic acids (Buu-Hoï, *Compt. rend.*, 1941, **212**, 242, 268), *o*-benzoylbenzoic acid (Hantzsch and Schweite, *Ber.*, 1916, **49**, 213; Schmid *et al.*, *loc. cit.*), and benzil-*o*-carboxylic acid (Schmid *et al.*, *loc. cit.*), and their esters. This method can also be applied to αβ-unsaturated γ-keto-acids such as β-acetylacrylic acid (Shaw, *J. Amer. Chem. Soc.*, 1946, **68**, 2510), although some disagreement exists in the case of penicillic acid (Shaw, *loc. cit.*; Raphael, *loc. cit.*). A disadvantage of the method is that prediction of the absorption curve for a new compound is difficult even if the structure is known, and model compounds of known structure are usually necessary for purposes of comparison. Little useful information concerning structure can be obtained from the ultra-violet absorption spectra of saturated keto-acids.

Since a reliable general method for the study of keto–lactol tautomerism was lacking, we turned our attention in 1947 to infra-red absorption spectroscopy, which at that time had not been used for this purpose. However, while this work was in progress, the application of infra-red spectroscopy to the study of tautomerism in penicillic acid was reported by Munday (*Nature*, 1949, **163**, 443).

Initially it was hoped that, providing there were no complicating factors such as the presence in the molecule of additional carbonyl groups, the normal and *pseudo*-esters could be distinguished by a simple qualitative test, the normal esters showing two absorption bands, one due to the ester and the other to the ketonic C=O group, and the *pseudo*-esters showing only one such band arising from the C=O in the lactone ring. Similarly it was hoped that acids in the open keto-form (I; R = H) could be recognised by two bands in the C=O region of the spectrum, whereas the presence of one such band together with an absorption frequency in the 3-μ. region, attributable to the alcoholic hydroxy-group, could be used to identify acids in the lactol form (II; R = H). In practice it was soon found that while the presence of a characteristic alcoholic hydroxy-group absorption was a reliable indication of the presence of an acid in the lactol form, a single band only in the C=O region could not be used for identification purposes, some open-chain acids and normal esters showing only a single broad absorption band, the characteristic frequencies of the two C=O groups being almost identical and the bands superimposed. A more detailed quantitative study of the problem was therefore attempted.

Experimental.

Infra-red Spectra.—The spectrometer was a modified Hilger D 209 instrument enclosed in an air-tight "Perspex" casing, the air within the case being circulated continuously over a suitable desiccant. By this means the water-vapour background in the C=O stretching region was reduced to almost negligible proportions and the determination of the positions of the C=O stretching bands greatly facilitated. All measurements were taken with a rock-salt prism. Calibration was made by interpolation between hydrocarbon bands of known frequency. In the region of 1700 cm.$^{-1}$ the calibration was considered accurate to ±3 cm.$^{-1}$, a slit width of 4 cm.$^{-1}$ being used; at 3000 cm.$^{-1}$ the calibration was considered accurate to ±10 cm.$^{-1}$, with a slit width of 20 cm.$^{-1}$.

Solid compounds were first dried *in vacuo* over phosphoric oxide, and the spectra were obtained in "Nujol" suspension between rock-salt plates. The suspensions were made by grinding the solids to fine powders in an agate mortar and then stirring the powder with "Nujol." When acids were being examined the melting points of the compounds were taken before and after grinding; no differences were noted and no effects analogous to those described by Munday (*loc. cit.*) for penicillic acid were observed. Liquids indicated in the Tables by an asterisk were examined in cells of 0·01-mm. thickness.

Materials.—With few exceptions, listed below, the organic compounds examined were prepared by literature methods and purified by crystallisation or distillation.

Normal methyl *o*-formylbenzoate, b. p. 130°/10 mm., was obtained by Rosenmund reduction of the acid chloride from methyl hydrogen phthalate although the yields claimed by Eliel and Burgstahler

(*J. Amer. Chem. Soc.*, 1949, **71**, 2251) were not realised. It formed a semicarbazone, obtained as needles, m. p. 194°, from methanol (Found: C, 54·2; H, 5·3; N, 18·8. Calc. for $C_{10}H_{11}O_3N_3$: C, 54·3; H, 5·0; N, 19·0%).

Benzil-o-carboxylic acid pseudo*acetate*. Benzil-*o*-carboxylic acid (lactol form; 0·3 g.) was suspended in acetic anhydride (2 c.c.) and one drop of concentrated sulphuric acid added. After 30 minutes the solution was poured into water, and the solid product crystallised from ethanol. It formed prisms, m. p. 138° (Found: C, 68·5; H, 4·3. Calc. for $C_{17}H_{12}O_3$: C, 68·9; H, 4·1%). Schmid, Hochweber, and von Halban (*loc. cit.*) give m. p. 137—138°.

Methyl ω-bromoacetophenone-o-carboxylate. A solution of the acid (25 g.; m. p. 113°) in dry methanol (100 c.c.) was saturated with hydrogen chloride at 0°. After 20 hours at room temperature the solvent was removed and the residual oil taken up in ether and washed with sodium hydrogen carbonate solution. The colourless oily residue solidified when kept and was crystallised from methanol; it formed plates (20·5 g.), m. p. 62° (Found: C, 46·8; H, 3·5; Br, 32·3. Calc. for $C_{10}H_9O_3Br$: C, 46·7; H, 3·5; Br, 31·1%).

Methyl ωω-dibromoacetophenone-o-carboxylate was prepared by the same method; it was obtained as plates, m. p. 122° (Found: C, 35·7; H, 2·4; Br, 46·8. $C_{10}H_8O_3Br_2$ requires C, 35·7; H, 2·4; Br, 47·6%). Gabriel (*Ber.*, 1907, **40**, 72) using essentially the same method reported the isolation of an ester, m. p. 112°, possibly identical with the above compound.

Results and Discussion.

Discussion of the spectra, which are not reproduced, is limited to the OH stretching (3—4 μ.) and double-bond stretching (5—7 μ.) regions.

It is well known that alcohols in very dilute solution show a characteristic sharp absorption band at about 3650 cm.$^{-1}$ associated with the " free " OH stretching vibration. If the solution is concentrated or the alcohol is examined in the solid state so that intermolecular " hydrogen bonding " can occur, the absorption band becomes broader and moves to lower frequency (about 3450 cm.$^{-1}$). Similar considerations apply to the OH stretching vibrations of carboxylic acids but the shift from the " free " vibration frequency of the monomeric form (3600 cm.$^{-1}$) to that of the solid dimeric form (2800—2500 cm.$^{-1}$) is very much greater.

In general the spectrum of an organic compound is most satisfactorily obtained in solution. Nevertheless, the interpretation of solution spectra of carboxylic acids is complicated by the persistance of the dimeric form. For example, with aliphatic acids, except in very dilute solution, bands are normally observed in the C=O stretching region both near 1760 cm.$^{-1}$ (monomer) and near 1720 cm.$^{-1}$ (bonded dimer). For the study of keto–lactol tautomerism, therefore, certain advantages were to be gained by an examination of solid samples; and in particular it appeared that the OH absorption frequencies of alcohols and carboxylic acids could be distinguished more readily. Some of the esters which it was desired to examine were in the liquid state at room temperature. However, there is some evidence that dipolar association occurs with simple esters in the liquid state (Hartwell, Richards, and Thompson, *J.*, 1948, 1436) and therefore the shifts to the carbonyl absorption bands of these compounds on passing from the solid to the liquid state would be expected to be small. It follows that valid conclusions may be drawn from comparisons between solid and liquid esters of the same general type.

The structures of the esters of *o*-formylbenzoic acid are readily established by chemical methods. The liquid normal ester, b. p. 130°/10 mm., shows reactions typical of an aromatic aldehyde including the ready formation of derivatives with carbonyl reagents—reactions which are absent in the *pseudo*-ester (3-methoxyphthalide), m. p. 46—47°. The OH and C=O absorption frequencies found for *o*-formylbenzoic acid, m. p. 98°, and its normal and *pseudo*-methyl esters are compared with phthalide, benzoic acid, and methyl benzoate in Table I. The figures for the C=O absorptions of benzoic acid and its methyl ester agree well with those previously reported (Davies and Sutherland, *Nature*, 1938, **141**, 372; Hartwell, Richards, and Thompson, *loc. cit.*). The broad absorption band with maxima at 2618 and 2538 cm.$^{-1}$ in benzoic acid is attributed to the OH stretching vibration of the carboxyl group.

Table I.

Compound.	Frequency (cm.$^{-1}$). C=O.	OH.	Compound.	Frequency (cm.$^{-1}$). C=O.	OH.
Phthalide	1750	—	Benzoic acid	1690	2618 2538
o-Formylbenzoic acid	1738	3250	Methyl benzoate *	1724	—
o-Formylbenzoic acid, *pseudo*-methyl ester	1768	—	Normal methyl *o*-formylbenzoate *	1725 1708	—

The normal methyl ester of *o*-formylbenzoic acid showed a broad absorption band in the C=O region just resolvable into two peaks at 1725 and 1708 cm.$^{-1}$, attributable to aromatic ester

and aromatic aldehyde C=O, respectively. The *pseudo*-ester showed only a single band, as was to be expected, at a frequency appreciably higher (1768 cm.$^{-1}$) than that of the ester C=O in the normal methyl ester. From the single C=O absorption band at 1738 cm.$^{-1}$, much closer to the five-ring lactone frequency of phthalide (1750 cm.$^{-1}$) than to the aromatic carboxylic acid (1690 cm.$^{-1}$) frequency of benzoic acid, and from the characteristic alcoholic OH absorption, it is clear that *o*-formylbenzoic acid exists in the lactol form in the solid state.

A number of simple related keto-acids, listed in Table II, were also found to be in the lactol form in the solid state. In some cases the alcoholic OH frequencies were somewhat lower than expected and this effect is discussed more fully later.

TABLE II.

Compound.	M. p.	Frequency (cm.$^{-1}$). C=O.	OH.
Phthalonic acid	144°	{1765} {1725}	3472
Acetophenone-*o*-carboxylic acid	116—118	1732	3205
ω-Bromoacetophenone-*o*-carboxylic acid	122—123	1740	3165
ωω-Dibromoacetophenone-*o*-carboxylic acid	131—132	1740	3165

Among more complex molecules containing carbonyl groups in addition to those involved in ring-chain tautomerism, the colourless, lactol form, m. p. 125—130°, and the yellow keto-form, m. p. 142° (Graebe and Juillard, *Ber.*, 1888, **21**, 2003; Hantzsch and Schweite, *loc. cit.*), of benzil-o-carboxylic acid were examined, as was the yellow normal methyl ester, m. p. 118° (Schmid, Hochweber, and von Halban, *loc. cit.*) of this acid. Unfortunately, attempts to prepare the unknown *pseudo*-methyl ester failed. The results obtained (Table III) support the conventional structural formulation of the above compounds, the lactol form of the acid showing typical alcoholic and the keto-form typical carboxylic acid type OH absorption.

TABLE III.

Compound.	Frequency (cm.$^{-1}$). C=O.	OH.
Benzil-*o*-carboxylic acid (lactol)	{1745} {1692}	3268
Benzil-*o*-carboxylic acid (keto)	{1698} {1683}	2632 2513
Benzil-*o*-carboxylic acid normal methyl ester	{1713} {1680}	— —

The bands at 1680 and 1692 cm.$^{-1}$ in benzil-*o*-carboxylic acid normal methyl ester and benzil-*o*-carboxylic acid (lactol), respectively, are attributed to aromatic ketone C=O; those at 1713 and 1745 cm.$^{-1}$ to aromatic ester and phthalide ring lactone C=O, respectively. In the keto-form of benzil-*o*-carboxylic acid the frequencies characteristic of aromatic ketone and aromatic carboxylic acid are too close together to allow definite band assignment.

As may be seen by inspection of Tables I—III, the keto- and the lactol form of carboxylic acids are readily recognised from the infra-red absorption data. With the esters of these acids, distinction is not so clear cut.

In the two examples where an α-diketone grouping occurs, the conjugation of one C=O group with a second has no effect on the absorption frequency. Since the two ketonic groups are equivalent, or very nearly so, in the normal methyl ester of benzil-*o*-carboxylic acid, the substance shows only two absorption bands. Two bands would also be expected from the *pseudo*-ester, so that in this particular case, structures could not have been allocated from the number of bands observed. Owing to the superposition of the carbonyl absorption bands, the normal ester of *o*-formylbenzoic acid is only just recognisable as such from the infra-red spectrum. At this stage of the investigation it was realised that in the case of esters of aromatic γ-keto-acids, the actual frequency of the C=O absorption always gave sufficient and reliable indication of the structure of the compound, the C=O in the phthalide ring of the *pseudo*-esters absorbing in the range 1740—1770 cm.$^{-1}$ whereas the normal esters absorbed much below these values (1710—1730 cm.$^{-1}$).

The correlation of vibrational spectra with characteristic groupings is due largely to the work of Barnes *et al.* (Barnes, Gore, Liddel, and Williams, "Infra-red Spectroscopy" Reinhold Publishing Corp., New York, 1944: *Anal. Chem.*, 1948, **20**, 402) and of Thompson (*J.*, 1948, 328), and it has been shown that with some linkages, small alterations in the attached atoms or linkages produce small but characteristic displacements of the absorption bands. In the case of the C=O link these effects have been studied by Lecomte in a series of papers between 1941 and 1945, by Thompson and Torkington (*J.*, 1945, 640), and by Hartwell, Richards, and

Thompson (*loc. cit.*). Correlations between absorption frequency and specific types of carbonyl group in steroids have been reported by Jones, Williams, Whalen, and Dobriner (*J. Amer. Chem. Soc.*, 1948, **70**, 2024) and Jones, Humphries, and Dobriner (*ibid.*, 1949, **71**, 241); and Rasmussen, Tunnicliff, and Brattain (*ibid.*, 1949, **71**, 1068, 1073) have published much valuable data on ketones and carboxylic acid derivatives. Additional data have been obtained on esters by Hampton and Newell (*Anal. Chem.*, 1949, **21**, 914) and on lactones by Thompson and Richards ("Chemistry of Penicillin," Princeton Univ. Press, 1949, p. 386).

The characteristic frequencies of the carbonyl groups in various types of aldehydes, ketones, esters, lactones, and acids, largely taken from the recent literature mentioned above, are summarised in Table IV. With aldehydes, ketones and carboxylic acids, conjugation with C=C or the benzene nucleus produces shifts of 30—40 cm.$^{-1}$ or 20—30 cm.$^{-1}$, respectively, to lower frequencies. With lactones and esters these shifts to lower frequencies on conjugation are rather less pronounced. A shift of 25—30 cm.$^{-1}$ to higher frequencies occurs on passing from a six-membered ring to the corresponding five-membered ring compound, due to the increased strain in the ring. It cannot be emphasised too strongly that the frequencies tabulated apply only to the simplest compounds in which it is possible to vary ring size and the type of conjugation. In more complex molecules the C=O frequencies can be modified very considerably by the presence of substituents (cf. Flett, *Trans. Faraday Soc.*, 1948, **44**, 767), and either an inductive or an electromeric mechanism may be involved. Electron-attracting substituents cause shifts to higher frequencies. Interaction effects resulting in the displacement of the carbonyl absorption bands to higher frequencies have also been observed when two carbonyl groups occur in the 1 : 2-, 1 : 3-, or 1 : 4-positions relative to one another (Jones, Humphries, and Dobriner, *loc. cit.*). Still greater shifts to lower frequencies can occur in molecules containing hydroxyl groups, capable of interacting with the carbonyl groups, the magnitude of the effect depending on whether the hydrogen bonding is intermolecular or intramolecular (chelation).

TABLE IV.

Frequency–structure correlations for the C=O stretching vibration.

Ketones.	Frequency (cm.$^{-1}$).
Acyclic, unconjugated	1715
Acyclic, $\Delta^{\alpha\beta}$	1670
In six-membered ring, unconjugated	1720
In six-membered ring, $\Delta^{\alpha\beta}$	1680
In five-membered ring, unconjugated	1745
In five-membered ring, $\Delta^{\alpha\beta}$	1715
In five-membered ring, $\Delta^{\beta\gamma}$	1755
Aryl alkyl	1690
Diaryl	1660
Aldehydes.	
Unconjugated	1730
$\Delta^{\alpha\beta}$	1695
Aromatic	1705

Esters.	Frequency (cm.$^{-1}$).
Unconjugated	1740
$\Delta^{\alpha\beta}$	1720
Aromatic	1720
Vinyl esters	1770
Phenyl esters	1765
Lactones.	
In six-membered ring, unconjugated	1740
In five-membered ring, unconjugated	1770
In five-membered ring, $\Delta^{\alpha\beta}$	1750
In five-membered ring, $\Delta^{\beta\gamma}$	1800
Phthalide ring	1750
Acids (solid dimer).	
Unconjugated	1715
$\Delta^{\alpha\beta}$	1680
Aromatic	1690

TABLE V.

C=O *absorption frequency* (*cm.*$^{-1}$) *in esters of γ-aldehydic and -ketonic acids.*

Parent acid (open form).	R = H.		R = Alkyl.		R = Aryl.	
	normal.	*pseudo.*	normal.	*pseudo.*	normal.	*pseudo.*
o-C_6H_4(COR)(CO$_2$H)	1705	1750	1690	1750	1660	1750
	1720		1720		1720	
CH·COR ‖ CH·CO$_2$H	1695	1750	1670	1750	1660	1750
	1720		1720		1720	
CH$_2$·COR | CH$_2$·CO$_2$H	1730	1770	1715	1770	1690	1707
	1740		1740		1740	

The C=O absorption frequencies, predicted from Table IV for the normal and *pseudo*-esters of some simple aldehydic and ketonic acids are set out in Table V. In every case the *pseudo*-

esters may be recognised by the high-frequency five-membered ring lactone C=O absorption (cf. Table I). In more complex molecules, provided something is known about the structure, due allowance may be made for the effects of substituents, where necessary by comparison with model compounds. These effects are discussed further below.

When, however, similar tables are drawn up for esters of β-aldehydic and -keto-acids it is found that the positions of the C=O absorption bands due to normal ester and six-ring lactone are identical, and in this series therefore, the esters could only be distinguished by the number of absorption bands recorded in the C=O stretching region, assuming that the necessary degree of resolution had been achieved, and that there were no complicating factors due to the presence of additional carbonyl groups.

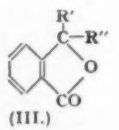
The effect of substitution in the 3-position on the absorption frequency of the phthalide (III) ring C=O is brought out in Table VI. The effect of nuclear substitution has not been studied. Electron-attracting substituents, such as carboxyl and methoxyl, give rise to shifts of 10—20 cm.$^{-1}$ to higher frequencies; the effect of the electron-repelling methyl group is negligible. Rather surprisingly, from the electronic view-point, a hydroxyl substituent in the 3-position causes an apparent shift of 10 cm.$^{-1}$ to lower frequencies, a difference of 20—30 cm.$^{-1}$ compared with the corresponding methylated compound. It is suggested that this effect is due to intermolecular hydrogen bonding, the hydroxy-group of one molecule interacting with the phthalide-ring keto-group of a second molecule and resulting in the lowering of both the C=O and OH frequencies. The OH frequencies do in fact appear close to 3200 cm.$^{-1}$ instead of at the normal bonded-hydroxyl value of 3450 cm.$^{-1}$. An interesting exception is phthalonic acid where the phthalide ring C=O and OH frequencies occur at the normal values of 1765 cm.$^{-1}$ and 3472 cm.$^{-1}$, respectively. Clearly in this case dimerisation only involves bonding between the carboxylic acid groups in the side-chain.

TABLE VI.

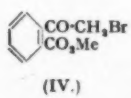
Absorption frequencies (cm.$^{-1}$) of phthalides (III).

R′.	R″.	C=O in ring.	Other C=O groups present.	Alcoholic OH.	R′.	R″.	C=O in ring.	Other C=O groups present.	Alcoholic OH.
H	H	1750	—	—	OH	H	1738	—	3250
OMe	H	1768	—	—	OH	CH_3	1732	—	3205
					OH	CH_2Br	1740	—	3165
OMe	CH_2Br	1760	—	—	OH	$CHBr_2$	1742	—	3165
OMe	$CHBr_2$	1772	—	—	OH	COPh	1745	1692	3268
H	CO_2H	1775	1718	—	OAc	COPh	1745	1712	—
					3-Methylenephthalide		1780	—	—
OH	CO_2H	1765	1725	3472	Phthalidylideneacetic acid		1800	1705	—

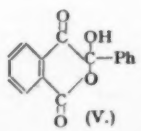
Methyl ω-bromoacetophenone-*o*-carboxylate, m. p. 62°, probably identical with the ester, m. p. 61—62°, described by Gabriel (*Ber.*, 1907, **40**, 72) and assigned the open structure (IV), shows a single C=O absorption band at 1760 cm.$^{-1}$ and therefore should be formulated as (III; R′ = OMe, R″ = CH_2Br).



(III.)



(IV.)

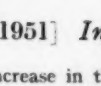


(V.)

Similarly, esterification of ωω-dibromoacetophenone-*o*-carboxylic acid with methanolic hydrogen chloride gave a methyl ester, m. p. 122°, with a single C=O absorption frequency at 1772 cm.$^{-1}$ and therefore clearly the *pseudo*-ester (III; R′ = OMe, R″ = $CHBr_2$). It is also apparent from a consideration of the frequency–structure correlations in Table IV that the lactol form of benzil-*o*-carboxylic acid has the structure (III; R′ = OH, R″ = COPh) and not the alternative six-ring lactol formula (V).

3-Methylenephthalide and phthalidylideneacetic acid are included in Table VI because of the high frequency of the ring C=O absorption. Both contain the $-C=C-O-CO-$ grouping present in vinyl and phenyl esters (Table IV), and the increase in frequency has been attributed to the

increase in the electron-attracting power of the oxygen atom adjacent to the double bond (Hartwell, Richards, and Thompson, *loc. cit.*; Walsh, *Trans. Faraday Soc.*, 1947, **43**, 75). Interaction effects resulting in the displacement of one of the C=O bands to higher frequency are observed in benzil-*o*-carboxylic acid *pseudo*-acetate (III; R′ = OAc, R″ = COPh). This compound contains the grouping (inset) present in the 21-acetoxy-20-keto-steroids studied by Jones *et al.* (*loc. cit.*) and found to show similar shifts due to interaction of the C=O groups.



In the present paper only esters of aromatic acids have been investigated but it is hoped to extend the work to other types in later papers. The application of the method to gladiolic acid and its derivatives will be discussed in Part III.

Microanalyses were carried out by Drs. Weiler and Strauss, Oxford, and by Mr. W. Brown. We are indebted to Dr. T. P. C. Mulholland for the preparation of some of the compounds examined, and to the Directors of Imperial Chemical Industries Limited, Plastics Division, for permission to publish this work.

IMPERIAL CHEMICAL INDUSTRIES LIMITED, BUTTERWICK RESEARCH LABORATORIES,
THE FRYTHE, WELWYN, HERTS.
IMPERIAL CHEMICAL INDUSTRIES LIMITED, PLASTICS DIVISION,
WELWYN GARDEN CITY, HERTS. [*Received, November 3rd*, 1950.]

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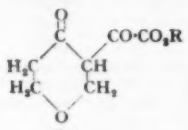
197. *Infra-red Spectroscopy and Structural Chemistry. Part II.* iso*Clavacin and Patulin.*

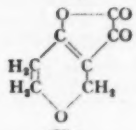
By JOHN FREDERICK GROVE.

The infra-red absorption spectra of *iso*clavacin and patulin have been examined, and the structures of these compounds are discussed in the light of these results and others obtained with suitable model substances.

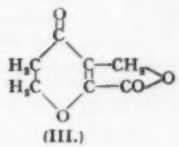
TREATMENT of 3-ethoxalyltetrahydro-4-pyrone (I; R = Et) with a hydrogen halide in acetic acid in the presence of a small amount of water has been shown by Cohen *et al.* (B.P. 610,859; cf. *Chem. and Ind.*, 1949, 640) to yield a compound, $C_7H_8O_4$, m. p. 87°, isomeric with the antibacterial mould product patulin.



(I.)

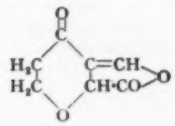


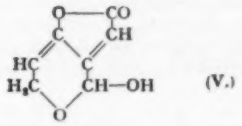
(II.)



(III.)

(IV.)

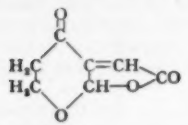




(V.)

Two possible structures were considered for this isomer: (II), derived from (I) by enolisation and lactonisation, and (III), in which, after initial opening of the tetrahydropyrone ring of (I), enolisation of the β-diketone system has occurred in the opposite direction and has been followed by lactonisation and ring closure to the dihydropyrone. The chemical evidence recently reported by Cohen (*Chem. and Ind., loc. cit.*) favours (III); moreover, the compound is stated to be identical with that obtained by Puetzer, Nield, and Barry (*Science*, 1945, **101**, 307; *J. Amer. Chem. Soc.*, 1945, **67**, 832) by the cyclisation of α-keto-β-β′-methoxypropionylbutyrolactone with sulphuric acid and called *iso*clavacin. The possible conversion of (I) into (III) by the above mechanism suggests that we are dealing with a system of high mobility, in which the determination of structure by the use of chemical reagents and by observation of chemical reactions may be open to criticism. It is perhaps relevant that the structural formulæ, (IV), (V), and (VI), proposed for patulin by Raistrick, Birkinshaw, Michael, and Bracken (*Lancet*, 1943, **245**, 625; see also Bergel, Morrison, Moss, and Rinderknecht, *J.*, 1944, 415), Woodward

and Singh (*J. Amer. Chem. Soc.*, 1949, **71**, 758), and Engel, Brzeski, and Plattner (*Helv. Chim. Acta*, 1949, **32**, 1166, 1752) respectively, may all be derived from β-formyl-β-β′-hydroxypropionyl-



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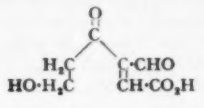

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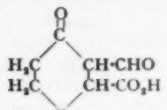


(VIIa.)

acrylic acid (VII) by the elimination of a molecule of water. [Woodward and Singh (*Experientia*, 1950, **6**, 238) have recently discussed this aspect of the problem more fully.] The formation of (IV) involves the cyclic form (VII*a*). The cyclisation of $\Delta^{\gamma\delta}$-carboxylic acids to the corresponding saturated lactones is well known; similar phenomena may occur with unsaturated alcohols in which the double bond is suitably polarised, and there is some evidence that certain substituted allyl alcohols exist in cyclic form (Hills, Kenyon, and Phillips, *Chem. and Ind.*, 1933, **52**, 660).

Accordingly, it seemed desirable to investigate physical methods capable of distinguishing between (II) and (III), which did not involve solution of the compound in a hydrolytic solvent; infra-red absorption spectroscopy was an obvious choice.

The published ultra-violet absorption data for *iso*clavacin ($\lambda_{max.} = 276$ mμ.; $\log \varepsilon = 3{\cdot}97$) strongly suggest the presence of a system consisting of three conjugated chromophores, and favour (III). Structure (IV) for patulin ($\lambda_{max.} = 277$ mμ.; $\log \varepsilon = 4{\cdot}22$) is also unlikely on the ultra-violet absorption evidence.

TABLE I.

Structure.	Grouping.	Predicted frequency (cm.$^{-1}$).
(II)	$\Delta^{\beta\gamma}$ five-membered ring lactone C=O	1800
	$\Delta^{\alpha\beta}$ five-membered ring ketone C=O	1715
(III)	$\Delta^{\alpha\beta}$ five-membered ring lactone C=O	1750
	$\Delta^{\alpha\beta}$ six-membered ring ketone C=O	1680
(IV)	$\Delta^{\beta\gamma}$ five-membered ring lactone C=O	1800
	$\Delta^{\alpha\beta}$ six-membered ring ketone C=O	1680
(V)	OH	3200—3450
	$\Delta^{\alpha\beta}\Delta^{\gamma\delta}$ (exocyclic) five-membered ring lactone C=O	1770 *
(VI)	$\Delta^{\alpha\beta}$ five-membered ring lactone C=O	1750
	$\Delta^{\alpha\beta}$ six-membered ring ketone C=O	1680

* The nearest available model for this lactone is 3-methylenephthalide (Grove and Willis, preceding paper) which absorbs at 1780 cm.$^{-1}$. The figure 1770 cm.$^{-1}$ is obtained by subtracting 10 cm.$^{-1}$ to allow for the superior conjugating effect of the ethylenic C=C as compared with the benzene nucleus.

Recent work on the characteristic stretching vibrations of carbonyl groups (summarised in Part I, preceding paper) has enabled reliable correlations to be made between the C=O absorption frequency and structure. The C=O and OH stretching frequencies, predicted for compounds of structures (II)—(VI) by use of these correlation rules, are included in Table I and the values actually observed for patulin and *iso*clavacin in Table II.

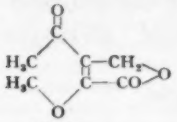
TABLE II.

	Frequency (cm.$^{-1}$).			Frequency (cm.$^{-1}$).	
	C=O.	OH.		C=O.	OH.
*iso*Clavacin	1768, 1688	—	Patulin	1768, 1745 *	3390

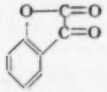
* "Shoulder" to main absorption band.

The high-frequency band associated with the $\beta\gamma$-unsaturated five-membered lactone ring of formula II is not observed, and the tables provide additional support for the view that *iso*clavacin is (III), although the agreement between the observed frequencies and those predicted for this structure is only fair. However, the total shift associated with the conjugating effect of an ethylenic double bond was taken into account in calculating the absorption frequencies of both C=O groups of (III); it would be more reasonable to assume that the C=C which is common to the C=O groups would not exert its full effect on both, and the lactone C=O absorption does in fact fall closer to that normally associated with an unconjugated five-membered ring lactone (1770 cm.$^{-1}$).

The results for patulin favour structure (V) and are in good agreement with those published by Woodward and Singh (*loc. cit.*). In particular, the strong, alcoholic OH absorption at



(VIII.)



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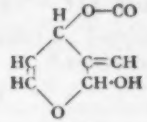


(X.)

3390 cm.$^{-1}$ provides additional evidence.* It is not easy to account for the shoulder at 1745 cm.$^{-1}$ but taken in conjunction with another weak band at 1680 cm.$^{-1}$, which may be due to C=O or C=C, it may indicate the presence of a small percentage of another structure such as (X). Alternatively it is possible that there is intermolecular hydrogen bonding between C=O and OH groups of the type discussed in the preceding paper, involving a small proportion of the molecules only, and that this type of dimerisation persists in solution and therefore appears in the solution spectra obtained by Woodward and Singh.

Additional evidence in support of (III) for *iso*clavacin has been obtained from examination of the model compounds, β-acetyl-α-methoxy-$\Delta^{\alpha\beta}$-butenolide (VIII) and coumaran-2 : 3-dione (IX) (cf. Table III).

TABLE III.

	Grouping.	C=O Stretching frequency. Predicted.	Found.
(VIII)	$\Delta^{\alpha\beta}$ five-membered ring lactone C=O	1750	1770
	$\Delta^{\alpha\beta}$ acyclic ketone C=O	1670	1670
(IX)	lactone C=O } see below	1810	1833
	ketone C=O } see below	1730	1740

The spectrum of (VIII) was practically identical with that of *iso*clavacin in the double-bond stretching region. The arguments used above in the case of *iso*clavacin may be applied to account for the apparent discrepancy between the observed and predicted values of the lactone ring C=O vibration.

In attempting to predict the C=O frequencies for coumaran-2 : 3-dione, 10 cm.$^{-1}$ have been added to those estimated for (II) to allow for the weaker conjugating effect of the benzene nucleus compared with that of an ethylenic double bond. The observed frequencies are appreciably higher, perhaps because of the greater strain in the heterocylic ring or more probably because of some electronic or interaction effect analogous to that observed in pyruvic acid and methyl pyruvate. In the latter compound the ketone C=O absorption is shifted to a frequency (1745 cm.$^{-1}$) some 30 cm.$^{-1}$ higher than the normal value (1715 cm.$^{-1}$) for an unconjugated acyclic ketone (cf. Randall, Fowler, Fuson, and Dangl, "Infra-red Determination of Organic Structures," van Nostrand, New York, 1949, p. 166).

EXPERIMENTAL.

Infra-red Spectra.—These were obtained using the modified Hilger D 209 instrument described in the preceding paper. β-Acetyl-α-methoxy-$\Delta^{\alpha\beta}$-butenolide was examined as a liquid, the other compounds as powders in "Nujol" suspension.

Materials.—Authentic specimens of patulin, m. p. 111°, and *iso*clavacin, m. p. 87°, were kindly supplied by Dr. A. Cohen. Coumaran-2 : 3-dione, yellow needles, m. p. 132°, was purified by crystallisation from benzene–light petroleum.

β-Acetyl-α-methoxy-$\Delta^{\alpha\beta}$-butenolide. This was obtained from Dr. A. L. Morrison who prepared it in the following manner :

β-Acetyl-α-ketobutyrolactone (4·12 g.) was added to an excess of diazomethane in ether, and the ether and excess of diazomethane were distilled off, leaving the *lactone* as an oil, b. p. 130°/13 mm. [$\lambda_{max.}$ (in methanol) = 270 mμ.; log ε = 4·08] [Found : OMe, 20·1%; equiv. (by titration), 156. $C_7H_8O_4$ requires OMe, 20·0%; equiv., 156].

I am indebted to Dr. F. Bergel for many interesting discussions on this work, to Dr. A. Cohen and Dr. A. L. Morrison, Research Department, Roche Products Ltd., for gifts of chemicals, and to Mr. H. A. Willis and the Directors of Imperial Chemical Industries Limited, Plastics Division, for the use of infra-red facilities.

IMPERIAL CHEMICAL INDUSTIRES LIMITED, BUTTERWICK RESEARCH LABORATORIES,
THE FRYTHE, WELWYN, HERTS. [*Received, November 3rd*, 1950.]

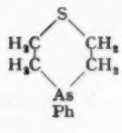
* While this paper was in preparation, Dauben and Weisenborn (*J. Amer. Chem. Soc.*, 1949, **71**, 3853) reported the presence of an OH band in the patulin spectrum.

198. *The Synthetic Application of Phenylarsinebis(magnesium Bromide). Part III. The Preparation and Properties of 4-Substituted Tetrahydro-1 : 4-oxarsines and of 1 : 4-Disubstituted Hexahydro-1 : 4-azarsines.**

By M. H. Beeby and Frederick G. Mann.

The above Grignard reagent reacts with di-(2-bromoethyl) ether to give tetrahydro-4-phenyloxarsine (II) and with bis-2-bromoethylaniline to give hexahydro-1 : 4-diphenylazarsine (VI). The properties of these novel heterocyclic compounds have been studied in some detail. It is noteworthy that the azarsine (VI) forms only monoquaternary salts, and evidence is adduced that this quaternisation occurs on the tertiary arsine group.

It has been shown by Job, Reich, and Vergnaud (*Bull. Soc. chim.*, 1924, **35**, 1404) that phenylarsinebis(magnesium bromide) reacted with 2 : 2′-dichlorodiethyl sulphide to give a resinous material, which on extraction with light petroleum furnished a 7% yield of the compound (I), which they termed phenylthiarsine (this would be termed tetrahydro-4-phenylthiarsine on the nomenclature system adopted in this paper). It formed crystals, m. p. 38°, b. p. 134°/14 mm. We find that the above Grignard reagent reacts with di-(2-bromoethyl) ether also to give a resinous product, which was largely unaffected by extraction with light petroleum; when,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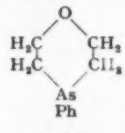
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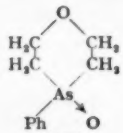
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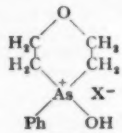
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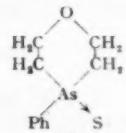

(V.)

however, this product was destructively distilled under reduced pressure, a series of three rather indefinite fractions was obtained; from the middle fraction tetrahydro-4-phenyloxarsine (II) was ultimately isolated. These results indicate that in both the oxygen and the sulphur series the initial reaction forms a complex product, probably owing to linear condensation of the dihalogeno-compound with the Grignard reagent, and that it is this product which on thermal decomposition gives the simple monocyclic derivative such as (II).

It is noteworthy that the first of the above fractions contained diethylphenylarsine. It is probable therefore that the secondary reaction (A) occurred (cf. Beeby, Cookson, and Mann, *J.*, 1950, 1917), and that the phenyldibromoarsine so formed then reacted with the ethyl-

$$2O(CH_2{\cdot}CH_2Br)_2 + AsPh(MgBr)_2 \longrightarrow 2Br{\cdot}CH_2{\cdot}CH_2{\cdot}O{\cdot}CH_2{\cdot}CH_2{\cdot}MgBr + AsPhBr_2 \quad (A)$$

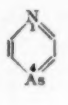
magnesium bromide—which was present in excess in the formation of the phenylarsinebis-(magnesium bromide)—to give diethylphenylarsine. In these circumstances the magnesium derivative $Br{\cdot}[CH_2]_2{\cdot}O{\cdot}[CH_2]_2{\cdot}MgBr$ would decompose and ultimately yield ethylene and

$$AsPh(MgBr)_2 + AsPhBr_2 \longrightarrow PhAs{:}AsPh + 2MgBr_2 \quad . \quad . \quad . \quad . \quad . \quad (B)$$

2-bromoethyl alcohol (cf. Tallman, *J. Amer. Chem. Soc.*, 1934, **56**, 126). In earlier experiments in which the excess of ethylmagnesium bromide was not used, the diethylphenylarsine was largely replaced as a by-product by arsenobenzene. It is reasonably certain that the latter is formed by the interaction of the phenylarsinebis(magnesium bromide) with the phenyldibromoarsine (reaction B), but that the latter compound reacts preferentially with ethylmagnesium bromide, when this is present in excess, to form diethylphenylarsine.

To isolate the pure tetrahydro-4-phenyloxarsine (II), the crude distilled product was oxidised

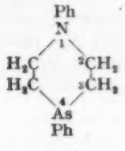
* These two novel heterocyclic systems are regarded as hydrogenated derivatives of the fundamental ring systems, 1 : 4-oxarsine (A) and 1 : 4-azarsine (B), respectively.

(A.)  (B.)

in acetone solution by hydrogen peroxide to the oxide (III), which was then precipitated as the crystalline hydroxy-picrate (IV; X = $C_6H_2O_7N_3$) since the latter could be readily purified by recrystallisation. This salt was then converted by hydrochloric acid into the hydroxy-chloride (IV; X = Cl), which on reduction gave the pure tetrahydro-4-phenyloxarsine (II), a colourless liquid having b. p. 149—151°/18 mm. It was characterised as its methiodide, systematically named tetrahydro-4-methyl-4-phenyl-1 : 4-oxarsinium iodide and as its palladochloride derivative, namely dichlorobis(tetrahydro-4-phenyloxarsine)palladium, $[(C_{10}H_{13}OAs)_2PdCl_2]$.

To obtain decisive evidence that the compound (II) had the simple six-membered ring, instead of possibly a twelve-membered ring, the oxide (III) was converted by hydrogen sulphide into tetrahydro-4-phenyloxarsine sulphide (V), a stable highly crystalline derivative the molecular weight of which in alcoholic solution confirmed the structure (V).

Di-(2-bromoethyl)aniline, $NPh(CH_2{\cdot}CH_2Br)_2$, reacts with phenylarsinebis(magnesium bromide) also to give a mixture of a crystalline and a resinous solid, the latter possibly also being the result of extensive linear reaction. Extraction of this mixture with hot light petroleum leaves the resin almost unaffected, but the extract yields the crystalline hexahydro-1 : 4-diphenyl-1 : 4-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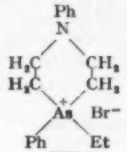
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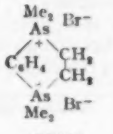
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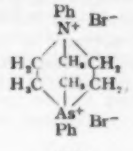
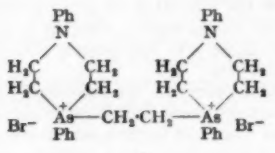

(IX.)

azarsine (VI), m. p. 97—97·5°, in 50% yield. This compound readily formed a monomethiodide, and when heated with an excess of ethyl bromide in a sealed tube at 100° formed only a monoethobromide (VII), the structure of which is discussed below: even with *p*-chlorophenacyl bromide (a very vigorous quaternising agent) only the monoquaternary salt was obtained.

It is known, however, that although *o*-phenylenebisdimethylarsine, $C_6H_4(AsMe_2)_2$, will form only a monomethobromide and methiodide (unpublished work), it will readily combine with ethylene dibromide to form the cyclic di(arsonium bromide) (VIII) (Glauert and Mann, *J.*, 1950, 682). Attempts were therefore made to combine the compound (VI) with one equivalent of ethylene dibromide to form the tricyclic diquaternary bromide (IX); again, however, each unit of (VI) underwent solely monoquaternisation, and the product was therefore *s*-ethylenebis(hexahydro-1 : 4-diphenylazarsinium) dibromide (X).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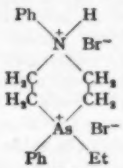
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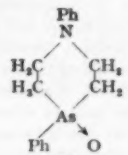
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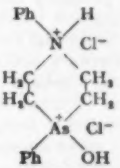

(XIII.)

The formulation of these various quaternary salts as arsinium salts instead of the isomeric ammonium salts rests on the following evidence.

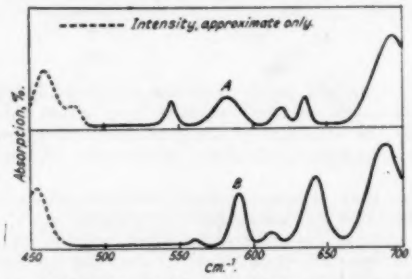
(i) It is common experience that a tertiary arsine will react with an alkyl halide much more readily than will the analogous tertiary amine, and this has been confirmed by careful measurement of the velocity of these quaternisations (Davis and Lewis, *J.*, 1934, 1599; Davis and Addis, *J.*, 1937, 1622).

(ii) The monoethobromide (VII) will form a monohydrobromide (XI). Clearly, had the initial quaternisation occurred on the nitrogen atom, the tertiary arsine group would have been neutral and therefore could not have formed a salt.

(iii) The azarsine when treated in acetone solution with very dilute hydrogen peroxide gave the oxide (XII). The structure of this compound is shown by the following facts: (*a*) the same compound was obtained by oxidation of the azarsine with chloramine-T, a reagent which readily oxidises tertiary arsines but leaves tertiary amines unaffected (Mann, *J.*, 1932, 958); (*b*) the oxide (XII) gave only a monopicrate, but gave a stable dihydrochloride (XIII) which

could be recrystallised from alcohol. It is clear that this strong acid gives a normal hydrochloride with the tertiary amine group and a hydroxy-chloride with the arsine oxide group. If the oxide had, however, been formed by oxidation of the tertiary amine group, the amine oxide would have given a hydroxy-chloride, but the tertiary arsine group would have been unaffected by the hydrochloric acid. This greater reactivity of the tertiary arsine group than of the tertiary amine towards oxidising agents would almost certainly be shown also towards quaternising agents.

(iv) The above chemical evidence, particularly (ii), places the constitution of these quaternary salts beyond doubt. Some confirmatory evidence from the infra-red absorption spectra has kindly been obtained by Dr. N. Sheppard, to whom we are indebted for the following report. " It was hoped to obtain infra-red spectroscopic evidence to help determine whether, in the crystalline methiodide of (VI), quaternisation had occurred on the amine or the arsine group. For this purpose, spectra were obtained in the potassium bromide region from 700 to 500 cm.$^{-1}$ for the above methiodide and also (for comparison) for phenyltrimethylarsonium iodide [$PhMe_3As$]I. The C–As linkages might be expected to have their stretching vibration frequencies in this region of the spectrum, as they occur at 572 and 584 cm.$^{-1}$ in trimethylarsine (Rosenbaum, Rubin, and Sandberg, *J. Chem. Physics*, 1940, **8**, 366). Should quaternisation have occurred at the arsenic atom of the compound (VI), it might be expected that the spectra of the two compounds would have some similarity in the region of the above stretching frequencies. The two spectra are shown in the annexed figure. The strong absorption bands above 650 cm.$^{-1}$



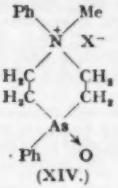
A. Methiodide of hexahydro-1 : 4-diphenyl-1 : 4-azarsine.
B. Phenyltrimethylarsonium iodide.

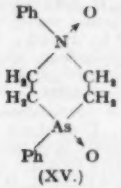
are probably caused by the phenyl group, but it appears likely that one or more of the other absorption bands in each spectrum can be associated with the vibration of C–As linkages. Although the two spectra are not sufficiently similar to decide unequivocally whether or not a quaternary arsenic atom is present in the methiodide of the arsine (VI), the general similarity would appear to be consistent with the presence of such a structure."

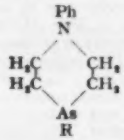
It is clear, therefore, that when the valency of the arsenic atom in the azarsine (VI) is increased to four, the tertiary nitrogen atom has its normal activity very considerably reduced. This effect appears (as would be expected) to be more marked when the tertiary arsine group is converted into a quaternary arsonium group than when it is converted into a tertiary arsine oxide. Further evidence on this point is provided by the arsine oxide (XII) which, when heated with an excess of methyl toluene-*p*-sulphonate at 100°, gave ultimately the quaternary salt (XIV; X = $C_7H_7{\cdot}SO_3$), which was characterised by conversion into the crystalline hydroxy-dipicrate. It is clear that the arsine oxide group under these vigorous conditions could not prevent quaternisation of the tertiary nitrogen group, yet no example was found of a similar quaternisation of the tertiary amine group when the tertiary arsine group had already been converted into a quaternary salt.

Furthermore, when the azarsine (VI) was oxidised with concentrated hydrogen peroxide it formed the dioxide (XV), which was undoubtedly formed by the further oxidation of the intermediate arsine oxide (XII): here, again, the tertiary amine group is not entirely inactivated by arsine oxide formation. It is noteworthy that the dioxide (XV) formed only a monopicrate. It is probable that in this salt it is the oxygen joined to the arsenic, and not that joined to the nitrogen, which has formed the hydroxy-group on combination with the picric acid, although there is no decisive evidence on this point: the significant fact is that both the oxide groups cannot simultaneously combine with a weak acid such as picric acid.

The general explanation of these results is probably closely parallel to that given by Mann and Watson (*J. Org. Chem.*, **1948**, **13**, 502), who pointed out that, for example, pyrazine forms only a monohydrochloride and a monomethiodide, whereas 1 : 4-dimethylpiperazine forms both a dihydrochloride and a dimethiodide. It was suggested that the electronic attraction exerted


(XIV.)


(XV.)


(XVI.)

by the strong positive pole on the first nitrogen atom of the pyrazine salts could be relayed readily by the mesomeric effect through the pyrazine ring to the second nitrogen atom, which was thus inactivated. When the dimethylpiperazine formed a monohydrochloride or a methiodide, this electronic attraction could be exerted only by the much weaker inductive effect through the saturated ring system, and the effect on the second nitrogen atom was too weak to cause inactivation. Many intermediate examples were given in tertiary amines, phosphines, and arsines of a positive pole on one of these atoms causing only a partial deactivation of a neighbouring and similar group, which therefore would, for example, give a stable hydrochloride but not a stable picrate.

In the case of 1 : 4-diphenylpiperazine, *i.e.*, the nitrogen analogue of our azarsine (VI), the two phenyl groups would in any case reduce the normal reactivity of the two nitrogen atoms compared with that of those in 1 : 4-dimethylpiperazine, and the diphenylpiperazine consequently forms only a monomethiodide (Dunlop and Jones, *J.*, 1909, **95**, 419). Precisely the same factors apply to our azarsine (VI) : the normal reactivity of the nitrogen atom would be reduced by the phenyl group, and the formation of a positive pole on the arsenic atom—by quaternisation or oxidation—would still further reduce this activity, a fact which is amply illustrated by the above examples.

One further point deserves comment. It has already been shown that the action of boiling hydriodic acid on a wide variety of heterocyclic tertiary arsines having an aryl group joined to the arsenic atom is to replace the aryl group by an iodine atom, the heterocyclic ring remaining unaffected (cf. Lyon, Mann, and Cookson, *J.*, 1947, 662; Beeby, Cookson, and Mann, *loc. cit.*; Beeby, Mann, and Turner, *J.*, 1950, 1923). The azarsine (VI) behaved similarly, with the formation of the cream-coloured crystalline hydriodide of the 4-iodo-1-phenyl derivative (XVI; R = I), which could be readily hydrolysed to the colourless 4-hydroxy-1-phenyl derivative (XVI; R = OH). When, however, the azarsine (VI) was boiled with hydriodic acid containing free iodine, the chocolate-brown crystalline hydriodide of the 4-tri-iodo-1-phenyl derivative (XVI; R = I_3) was formed : this was a stable compound which could be readily recrystallised, but when shaken with an aqueous solution of sulphur dioxide it was rapidly reduced to the above hydriodide of the monoiodo-derivative.

Experimental.

Tetrahydro-4-phenyl-1 : 4-oxarsine (II).—A solution of phenylarsinebis(magnesium bromide) was prepared by the action of a solution of phenylarsine (40 g.) in benzene (200 c.c.) on a Grignard reagent prepared from ethyl bromide (80 g., 2·8 mols.), ether (250 c.c.), and magnesium (18·8 g.) (cf. Beeby, Cookson, and Mann, *loc. cit.*). A solution of di-(2-bromoethyl) ether (57 g., 0·95 mol.) in benzene (100 c.c.) was added dropwise to the arsine Grignard reagent which was chilled and stirred for 2 hours. The product was then boiled under reflux for 2 hours, cooled, and hydrolysed with ammonium chloride solution, and the ethereal layer then separated, dried, and evaporated. The viscous residue was completely soluble in alcohol and hence contained very little (if any) arsenobenzene. Distillation at 0·1 mm. gave a small fraction at *ca.* 80° without decomposition, but the bulk of the distillate was obtained by slowly increasing the temperature of the bath to 250—300°, whereat contamination of the distillate with dark products of the decomposition became marked. Redistillation of this crude product at 20 mm. gave the fractions : (*a*) b. p. 110—130°, 10 g.; (*b*) b. p. 150—165°, 19 g.; (*c*) b. p. 165—190°, 4 g.

Fraction (*b*), which contained the major portion of the oxarsine, was dissolved in acetone, and the solution filtered to remove free arsenic and then oxidised with an excess of hydrogen peroxide (20-vol.). The solution, after concentration under reduced pressure, was treated with picric acid, the *tetrahydro-oxarsine hydroxy-picrate* (IV; X = $C_6H_2O_7N_3$) being precipitated; from alcohol this formed yellow crystals, m. p. 123° (Found : C, 40·9; H, 3·3; N, 9·2. $C_{16}H_{14}O_8N_3As$ requires C, 40·9; H, 3·4; N, 9·0%) (20·8 g., 18% based on the dibromo-ether).

The picrate in aqueous suspension was decomposed with hydrochloric acid, the picric acid extracted with ether, and the aqueous solution of the hydroxy-chloride (IV; X = Cl) divided into two portions:

(i) The major portion was reduced by a stream of sulphur dioxide in the presence of chloroform and a trace of potassium iodide. The liberated arsine dissolved in the chloroform which, when separated, dried, and distilled, gave *tetrahydro-4-phenyl-1 : 4-oxarsine* (II) as a colourless liquid, b. p. 149—151°/18 mm. (Found: C, 52·4; H, 5·9. $C_{16}H_{15}OAs$ requires C, 53·6; H, 5·85%) (the low carbon value was apparently due to oxidation). The arsine readily gave a *methiodide*, colourless crystals (from alcohol), m. p. 162—162·5° (Found: C, 35·9; H, 4·3. $C_{11}H_{14}OIAs$ requires C, 36·1; H, 4·4%), and also *dichlorobis(tetrahydro-4-phenyloxarsine)palladium*, which, after crystallisation first from ethanolic dioxan and then from dioxan, separated as orange crystals, m. p. 182°, containing 1 mol. of dioxan (Found: C, 40·0; H, 4·6. $C_{28}H_{28}O_3Cl_2As_2Pd,C_4H_8O_2$ requires C, 40·35; H, 4·8%).

(ii) The minor portion of the hydroxy-chloride solution was made alkaline with ammonia, evaporated to dryness, and extracted with chloroform. The extract was saturated with hydrogen sulphide, dried, and evaporated; the residue after crystallisation from alcohol furnished colourless crystals of *tetrahydro-4-phenyloxarsine sulphide* (V), m. p. 101·5—102° (Found: C, 47·0; H, 5·3%; *M*, ebullioscopic in 0·924% alcoholic solution, 253. $C_{16}H_{15}OSAs$ requires C, 46·9; H, 5·1%; *M*, 256).

Fraction (*a*) when treated with methyl iodide gave an impure methiodide, which could not be readily recrystallised; its solution in alcohol was therefore treated with sodium picrate, and the crude precipitated picrate, thrice recrystallised from alcohol, gave yellow crystals of *diethylmethylphenylarsonium picrate*, m. p. 81—81·5° (Found: C, 44·85; H, 4·2; N, 9·3. $C_{17}H_{20}O_7N_3As$ requires C, 45·0; H, 4·45; N, 9·3%). A sample of pure diethylphenylarsine was converted into the methopicrate, which when similarly recrystallised had m. p. 85—86°; a mixture of the two samples had m. p. 82—85·5°.

Fraction (*c*) when treated with methyl iodide, gave the methiodide of the oxarsine, m. p. 162° after three recrystallisations from alcohol (Found: C, 36·2; H, 4·54%). The difficulty in assessing the amount of arsine in fraction (*c*) prevented an accurate determination of the total yield.

Di-(2-bromoethyl)aniline.—Aniline was converted by ethylene chlorohydrin into di-(2-hydroxyethyl)-aniline, and the latter by phosphorus tribromide into di-(2-bromoethyl)aniline by Ross's method (*J.*, 1949, 183); the bromo-compound had m. p. 51—53° after recrystallisation from alcohol.

Hexahydro-1 : 4-diphenyl-1 : 4-azarsine (VI).—A solution of di-(2-bromoethyl)aniline (46·2 g.) in benzene (150 c.c.) was added slowly to a cooled, well-stirred solution of phenylarsinebis(magnesium bromide), prepared from phenylarsine (24·3 g., 1·05 mols.) and ethylmagnesium bromide. The mixture was stirred in the cold for 3 hours and then whilst boiling for 1·5 hours. After cooling and hydrolysis with aqueous ammonium chloride, the ethereal layer was collected, dried, and evaporated. The residue was thrice extracted with boiling light petroleum (b. p. 60—80°), and the united extracts were filtered and evaporated. The residue so obtained, when recrystallised from alcohol, gave the colourless *azarsine* (VI), m. p. 96—97·5° (Found: C, 64·4; H, 6·2; N, 5·05%; *M*, ebullioscopic in 1·181% alcohol solution, 272. $C_{16}H_{18}NAs$ requires C, 64·2; H, 6·1; N, 4·7%; *M*, 299); 22·8 g., 50% yield. The azarsine readily gave a *picrate*, yellow crystals (from alcohol), m. p. 172—173° (preliminary softening) (Found: C, 50·0; H, 4·3; N, 10·5. $C_{16}H_{18}NAs,C_6H_3O_7N_3$ requires C, 50·0; H, 4·0; N, 10·6%).

A solution of this azarsine in cold methyl iodide rapidly deposited the *monomethiodide*, colourless crystals (from alcohol), m. p. 181—182° (preliminary softening and darkening) (Found: C, 46·2; H, 4·55; N, 3·3. $C_{17}H_{21}NIAs$ requires C, 46·3; H, 4·8; N, 3·2%). The use of boiling methyl iodide gave the same product.

A mixture of the arsine and an excess of ethyl bromide was heated in a sealed tube at 100° for 6 hours. Evaporation gave a residue consisting solely of the *monoethobromide* (VII), colourless crystals, m. p. 179—179·5°, from ethyl acetate–alcohol (Found: C, 53·3; H, 6·0; N, 3·6. $C_{18}H_{22}NBrAs$ requires C, 52·9; H, 5·7; N, 3·5%). The addition of concentrated hydrobromic acid to a concentrated aqueous solution of this salt precipitated the *ethobromide hydrobromide* (XI), which after recrystallisation from alcohol formed colourless crystals, m. p. 207—208° (decomp.) (Found: C, 44·3; H, 5·3. $C_{18}H_{22}NBrAs,HBr$ requires C, 44·2; H, 4·95%). These slowly acquired a faint blue tint when stored.

A solution of the arsine (0·5 g.) and *p*-chlorophenacyl bromide (0·7 g., 2 mols.) in benzene (45 c.c.) was boiled for 4 hours. On cooling, a portion of the unchanged bromide was recovered. Evaporation of the solvent gave a syrup which could not be crystallised, but readily gave the *p-chlorophenacyl azarsinium picrate*, hygroscopic yellow crystals (from alcohol), m. p. 93—94° (Found: C, 52·8; H, 4·0; N, 8·0. $C_{30}H_{24}O_8N_4ClAs$ requires C, 52·9; H, 3·85; N, 8·2%).

A mixture of the azarsine (1·03 g.) and ethylene dibromide (0·65 g., 1 mol.) under nitrogen was heated at 115—120° for 5 hours. The product, thrice recrystallised from alcohol, gave the *diethanolate* of *s-ethylenebis(hexahydro-1 : 4-diphenyl-1 : 4-azarsinium) dibromide* (X), colourless crystals, m. p. 226—227° (decomp.) (Found: C, 51·8; H, 6·0; N, 3·6. $C_{34}H_{40}N_2Br_2As_2,2C_2H_6O$ requires C, 51·9; H, 6·0; N, 3·2%). This compound readily formed the corresponding unsolvated *dipicrate*, yellow crystals (from alcohol), m. p. 166—167° (preliminary decomp.) (Found: C, 51·2; H, 4·1; N, 10·8. $C_{46}H_{44}O_{14}N_8As_2$ requires C, 51·0; H, 4·1; N, 10·35%).

A similar reaction with trimethylene dibromide gave a viscous syrup which did not crystallise or give a crystalline picrate.

Oxidation of the Azarsine (VI).—(i) *With dilute hydrogen peroxide.* The addition of 0·6% hydrogen peroxide (30 c.c.) to a cold solution of the azarsine (1 g.) in acetone (30 c.c.) reprecipitated the arsine, which, however, slowly redissolved. Next day the solution was evaporated to dryness, and the colourless crystalline residue, when recrystallised from water, afforded the slightly hygroscopic *dihydrate* of the *azarsine oxide* (XII), m. p. 123—124° (Found: C, 54·2; H, 6·2. $C_{16}H_{17}ONAs,2H_2O$ requires C, 54·7; H, 6·3%). The dihydrate underwent considerable dehydration during storage in a vacuum over phosphoric anhydride for 5 days, but the product rapidly re-formed the dihydrate on exposure to damp air.

The oxide, treated in alcoholic solution with picric acid, gave the *azarsine hydroxy-picrate*, orange-red crystals (from alcohol), m. p. 188—189° (preliminary darkening) (Found : C, 48·2; H, 3·8; N, 10·4. $C_{22}H_{21}O_9N_4As$ requires C, 48·5; H, 3·9; N, 10·3%).

A solution of the oxide in an excess of hydrochloric acid was evaporated in a vacuum-desiccator, and the residue, once recrystallised from alcohol, gave colourless crystals of the *dihydrochloride* (XIII), m. p. 156—156·5° (Found : C, 49·3; H, 5·3; N, 3·9. $C_{16}H_{18}ONAs,2HCl$ requires C, 49·5; H, 5·2; N, 3·6%).

(ii) *With chloramine-T.* A solution of the azarsine (VI) (0·53 g.) and hydrated chloramine-T (0·5 g., 1 mol.) in alcohol (50 c.c.) was boiled under reflux for 1 hour, concentrated, cooled, and filtered to remove precipitated sodium chloride. The addition of alcoholic picric acid to the filtrate precipitated the above azarsine hydroxy-picrate, which after one recrystallisation from alcohol had m. p. 187·5—188·5°, unchanged by admixture with the previous sample.

(iii) *With concentrated hydrogen peroxide.* When an acetone solution of the azarsine (VI) was treated with an excess of 30% hydrogen peroxide and then kept at 50° for 3 hours, the dioxide (XV) was obtained as a syrup. When alcoholic solutions of this syrup and of picric acid were mixed, the *dioxide monopicrate* was precipitated, and after recrystallisation from alcohol was obtained as yellow crystals, m. p. 179° (preliminary decomp.) (Found : C, 47·1; H, 3·9; N, 10·2. $C_{16}H_{16}O_3NAs,C_6H_3O_7N_3$ requires C, 47·1; H, 3·8; N, 10·0%).

A mixture of the azarsine monoxide (XII) (0·2 g.) and methyl toluene-*p*-sulphonate (0·6 g., *ca.* 6 mols.) was heated in a sealed tube at 100° for 3 hours. Addition of ether to a concentrated alcoholic solution of the product precipitated an oil which slowly solidified. This solid, when recrystallised from alcohol–acetone, gave colourless crystals of the sulphonate (XIV; $X = C_7H_7{\cdot}SO_3$). For characterisation, these crystals in alcoholic solution were treated with picric acid, and the precipitate, when once recrystallised from alcohol, gave *hexahydro-4-hydroxy-1-methyl-1 : 4-diphenyl-1 : 4-azarsinium dipicrate* as yellow crystals, m. p. 182—183° (preliminary darkening) (Found : C, 44·9; H, 3·4; N, 12·4. $C_{29}H_{26}O_{15}N_7As$ requires C, 44·2; H, 3·3; N, 12·5%).

Action of Hydriodic Acid on the Azarsine (VI).—(i) A mixture of the azarsine (1 g.) and pure constant-boiling hydriodic acid (50 c.c.) was boiled under reflux in a carbon dioxide atmosphere for 2 hours, and the volume of acid then reduced by distillation under reduced pressure. The product was cooled, and the orange-coloured powder which had separated, when collected and recrystallised from methyl alcohol, furnished cream-coloured crystals of the *hydriodide*, m. p. 173—174° (decomp.), of *hexahydro-4-iodo-1-phenyl-1 : 4-azarsine* (XVI; R = I) (Found : C, 25·4; H, 3·2; N, 2·9. $C_{16}H_{18}NIAs,HI$ requires C, 25·2; H, 3·0; N, 2·9%). When this compound was shaken with a mixture of aqueous sodium hydrogen carbonate solution and chloroform, rapid decolorisation and dissolution occurred. The chloroform solution on evaporation gave a colourless crystalline residue, which after recrystallisation from *cyclo*hexane furnished the *hexahydro-4-hydroxy-azarsine* (XVI; R = OH), m. p. 116—116·5° (Found : C, 50·7; H, 5·9; N, 5·9. $C_{16}H_{14}ONAs$ requires C, 50·2; H, 5·9; N, 5·9%).

(ii) The above experiment was repeated with an old sample of hydriodic acid which was black with free iodine. Concentration of the acid solution now gave a dark deposit, which when collected, dried, and recrystallised from benzene furnished chocolate-brown crystals of the *hydriodide*, m. p. 136—138° (decomp.), of *hexahydro-4-tri-iodo-1-phenyl-1 : 4-azarsine* (XVI; $R = I_3$) (Found : C, 16·9; H, 2·2; N, 2·1. $C_{16}H_{18}NI_3As,HI$ requires C, 16·4; H, 1·9; N, 1·3%). These crystals, when treated in aqueous suspension with sulphur dioxide water, were rapidly converted into cream-coloured crystals of the above hydriodide of the 4-iodo-compound, which, after recrystallisation from methyl alcohol, had m. p. 173—175°, unchanged by admixture with the above compound. This process could be readily reversed : when hot benzene solutions of the hydriodide of the 4-iodo-compound and of iodine were mixed and cooled, the chocolate-brown crystals of the hydriodide, m. p. 134—138°, of the 4-tri-iodo-compound, rapidly separated.

We gratefully acknowledge a grant provided by the Department of Scientific and Industrial Research.

UNIVERSITY CHEMICAL LABORATORY, CAMBRIDGE. [*Received, November 9th*, 1950.]

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199. *The Action of Phthalide on Toluene-p-sulphonamide and its Derivatives.*

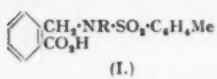
By DAVID H. PEACOCK.

Wislicenus (*Ber.*, 1885, **18**, 172; *Annalen*, 1886, **233**, 101) showed that potassium cyanide reacted with phthalide at 180—200° to form *o*-carboxybenzyl cyanide. It has now been found that the sodium derivatives of toluene-*p*-sulphonamide and of several of its monosubstituted derivatives react similarly, to give *N*-*o*-carboxybenzyltoluene-*p*-sulphonamide and similar *N*-substituted amides. From these derivatives the *N*-aryl-1-keto*iso*indolines are readily prepared.

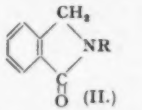
trans-1′-HYDROXY-2′-INDANYLACETIC ACID and the lactone of the *cis*-acid are not converted into amino-acids by the usual methods (Menon and Peacock, *J.*, 1934, 1297). In a search for

other methods of converting lactones into amino-acids preliminary experiments with phthalide and the sodium derivative of toluene-*p*-sulphonamide have shown that the toluene-*p*-sulphonyl derivative of the amino-acid is formed. Potassium phthalimide reacted similarly, but ethyl sodiomalonate gave only condensation products of malonic ester. The lactone of *cis*-1′-hydroxy-2′-indanylacetic acid decomposed below the temperature necessary for reaction. In the present paper the reactions with toluene-*p*-sulphon-amide and -anilide and some similar compounds are described.

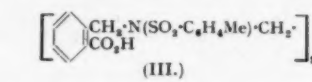
Wislicenus (*Ber.*, 1885, **18**, 172; *Annalen*, 1886, **233**, 101) showed that phthalide reacted at about 190° with potassium cyanide to form the potassium salt of *o*-carboxybenzyl cyanide. By analogy it would be expected that sodium or potassium, united with radicals capable of forming a stable linkage with carbon but not forming a too stable ion, might behave similarly.



(I.)



(II.)



(III.)

When the sodium derivative of toluene-*p*-sulphonamide was heated with phthalide at 180—200° the sodium salt of *N*-*o*-carboxybenzyltoluene-*p*-sulphonamide (I; R = H) was formed together with 1-keto-2-toluene-*p*-sulphonyl*iso*indoline (II; R = SO_2·C_6H_4Me). The sodium derivatives of toluene-*p*-sulphon-anilide, -*p*-toluidide, and -ethylamide similarly gave the analogous compounds (I; R = Ph, C_6H_4Me, and Et, respectively). *NN*′-Ditoluene-*p*-sulphonamidoethane gave a mixture of (I; R = CH_2·CH_2·NH·SO_2·C_6H_4Me) and (III).

Compounds of the type (I; R = Ph or C_6H_4Me) are readily converted by cold concentrated sulphuric acid into compounds of type (II), displacement of the toluene-*p*-sulphonyl group occurring during cyclisation. No such reaction occurs when toluene-*p*-sulphonanilide is treated with benzoic acid in concentrated sulphuric acid.

The derivatives described could presumably all be prepared by conventional methods from *o*-cyano- or *o*-carboxy-benzyl chloride but phthalide is more readily accessible and the reaction is of interest as an example of alkyl–oxygen fission of an ester (Day and Ingold, *Trans. Faraday Soc.*, 1941, **37**, 686).

Experimental.

N-*o*-*Carboxybenzyltoluene*-p-*sulphonamide*.—The sodium derivative of toluene-*p*-sulphonamide (10·0 g.) and phthalide (20·0 g., *ca.* 3 mols.) were well mixed and heated for 5 hours at 190—200° (oil-bath). They formed a sticky mass at about 180°. The cooled product, pink and slightly sticky, was extracted with warm ether, leaving a hard, pale yellow solid, which was extracted with warm sodium hydrogen carbonate (5 g. in 200 c.c. of water) and filtered, to give a yellow solid and a pink filtrate. Acidification of the filtrate with acetic acid afforded oily N-*o*-*carboxybenzyltoluene*-p-*sulphonamide* (6·7 g.), which soon solidified and crystallised from methanol, ethanol, or acetic acid as colourless needles, m. p. 162° (Found: C, 58·3; H, 4·81; N, 4·4; S, 10·1; equiv., 304. $C_{15}H_{15}O_4NS$ requires C, 59·0; H, 4·9; N, 4·59; S, 10·5%; equiv., 305). The yellow solid was extracted with warm ethanol, and residual 1-*keto*-2-*toluene*-p-*sulphonyl*iso*indoline* (3·7 g.) crystallised from acetic acid as colourless prisms, m. p. 211° (Found: C, 62·8; H, 4·8. $C_{15}H_{13}O_3NS$ requires C, 62·7; H, 4·5%), insoluble in aqueous sodium hydroxide.

N-*o*-*Carboxybenzyl*-N-*ethyltoluene*-p-*sulphonamide*.—The sodium derivative of *N*-ethyltoluene-*p*-sulphonamide (4·0 g.) was heated with phthalide (8·0 g.) for 3 hours at 170—190° (oil-bath). The product, worked up as above, gave N-*o*-*carboxybenzyl*-N-*ethyltoluene*-p-*sulphonamide* (4·1 g.), needles (from glacial acetic acid), m. p. 181° (Found: C, 61·1; H, 5·9. $C_{17}H_{19}O_4NS$ requires C, 61·2; H, 5·7%).

The Reaction applied to 1 : 2-*Ditoluene*-p-*sulphonamidoethane*.—The disodium derivative (4·0 g.) of this diamide and phthalide (8·0 g.) at 180—190° gave, in the usual way, a mixture of acids (5·0 g.). Extraction with alcohol left a residue. Addition of water to the alcoholic extract precipitated colourless 1-N-*o*-*carboxybenzyltoluene*-p-*sulphonamido*-2-*toluene*-p-*sulphonamidoethane* which, crystallised from acetone–benzene, had m. p. 166° (Found: C, 57·7; H, 4·9; N, 5·4. $C_{34}H_{34}O_6N_2S_2$ requires C, 57·3; H, 5·2; N, 5·6%). The residue from the alcohol, crystallised from acetic acid, afforded 1 : 2-*di*-(N-*o*-*carboxybenzyltoluene*-p-*sulphonamido*)*ethane*, m. p. 244° (decomp.; quick heating) (Found: C, 60·3; H, 5·0; N, 4·5. $C_{32}H_{32}O_8N_2S_2$ requires C, 60·3; H, 5·0; N, 4·4%).

N-*o*-*Carboxybenzyltoluene*-p-*sulphonanilide*.—The dry sodium derivative (4·0 g.) of toluene-*p*-sulphonanilide and phthalide (6·0 g.) at 170—190° (4 hours) gave the N-*o*-*carboxybenzyl* derivative (3·2 g.), m. p. 181° (from aqueous acetic acid) (Found: C, 66·1; H, 5·0. $C_{21}H_{19}O_4NS$ requires C, 65·9; H 5·2%).

N-*o*-*Carboxybenzyltoluene*-p-*sulphon*-p-*toluidide* was prepared similarly in 65% yield; it had m. p. 191° (from acetic acid) (Found: C, 66·7; H, 5·3; N, 3·3. $C_{22}H_{21}O_4NS$ requires C, 66·8; H, 5·3; N, 3·5%).

Substituted 1-*Keto*iso*indoline*.—*N-o*-Carboxybenzyltoluene-*p*-sulphonanilide (0·4 g.) in ice-cold,

concentrated sulphuric acid (2 ml.) was kept for 16 hours in a refrigerator. The mixture was then poured on ice and the 1-keto-2-phenyl*iso*indoline (0·3 g.) filtered off and crystallised from ethanol; it had m. p. 162° (Found: C, 79·8; H, 5·3. Calc. for $C_{14}H_{11}ON$: C, 80·4; H, 5·3%) (cf. Hessert, *Ber.*, 1877, **10**, 1450). The 2-p-*tolyl* derivative, prepared similarly, crystallised from alcohol in colourless plates, m. p. 140° (Found: C, 80·2; H, 5·8; N, 6·4. $C_{15}H_{13}ON$ requires C, 80·7; H, 5·8; N, 6·3%). The same product was obtained by the action of thionyl chloride on *N*-*o*-carboxybenzyltoluene-*p*-sulphon-*p*-toluidide. *N*-*o*-Carboxybenzyltoluene-*p*-sulphonethylamide was recovered unchanged from a solution in concentrated sulphuric acid kept at 0°, but was decomposed when this was heated at 100°.

UNIVERSITY OF SHEFFIELD. [*Received, November 29th*, 1950.]

200. *The Application of Lithium Alkynyls in the Synthesis of Long-chain Dialkylacetylenes.*

By B. B. ELSNER and P. F. M. PAUL.

The *n*-octadecynes have been synthesised in good yields and high purity, by metathetical reactions in liquid ammonia or dioxan, involving the appropriate lithium alkynyls and *n*-alkyl bromides. Further syntheses, of *n*-tricos-4-yne, *n*-octacos-9-yne, *n*-dotriacont-16-yne, and *n*-hexatriacont-17-yne, demonstrate that this method has wide application for the synthesis of dialkylacetylenes. An improved method for the preparation of lithium alkynyls is described, together with two modifications of the general method of synthesis of monoalkylacetylenes.

SEVERAL symmetrical dialkylacetylenes of low molecular weight have been prepared in good yield by Bried and Hennion (*J. Amer. Chem. Soc.*, 1937, **59**, 1310), who employed the simultaneous reaction in liquid ammonia between two mols. each of the appropriate *n*-alkyl bromides and one mol. each of sodium acetylide and sodamide. Later, however, they reported that the method was limited definitely to alkyl halides of small molecular weight and appreciable solubility in liquid ammonia. In the case of *n*-octyl bromide, for example, the yield of dialkylacetylene obtained under the best conditions was only 27%. These results have been confirmed during the present investigation.

We believed, however, that the diminished yields obtained from *n*-alkyl bromides of higher molecular weight were not entirely caused by their lower solubility but were more probably dependent largely on the lower solubility in liquid ammonia of the intermediate sodium alkynyls. Accordingly, the possibilities of using either a more suitable solvent, or a more soluble metal derivative, were investigated. The former approach failed since the sodium alkynyls were found to be only slightly soluble in the solvents investigated. With respect to the alternative, a literature survey revealed that the lithium alkynyls had not been extensively studied and we noted that, in general, the organometallic compounds of the first members of the metals in the same period exhibit certain abnormalities, particularly as regards solubility. Lithium alkynyls were found not only to be much more soluble in liquid ammonia than the sodium compounds, but also to be considerably more reactive. Following the procedure of Bried and Hennion (*loc. cit.*), *n*-octadec-9-yne was obtained in 60% yield from *n*-octyl bromide, lithium acetylide, and lithium amide in liquid ammonia.

This result led us to apply the reaction to syntheses of the unsymmetrical *n*-octadecynes (the 3-, 4-, 5-, 6-, 7-, and 8-isomers), which were obtained in yields of 78, 62, 52, 76, 76, and 67%, respectively. These syntheses were conducted conveniently on a 0·2 g.-mol. scale employing the normal two-stage method. The shorter alkyl group was substituted first by the method originally due to Lebeau and Picon (*Compt. rend.*, 1913, **156**, 1077), which has been used extensively by Vaughn, Vogt, Hennion, and Nieuwland (*J. Org. Chem.*, 1937, **2**, 1), and the lithium derivatives of these monoalkylacetylenes (but-1-yne, *n*-pent-1-yne, *n*-hex-1-yne, *n*-hept-1-yne, *n*-oct-1-yne, and *n*-non-1-yne) were then condensed with the appropriate *n*-alkyl bromides in liquid ammonia at room temperature.

The use of liquid ammonia as solvent for such metathetical reactions has many inherent disadvantages, the most obvious being manipulation. Attention was again directed, therefore, to the possible substitution of an alternative solvent. The lithium alkynyls, in marked contrast to the sodium alkynyls, were found to be freely soluble in anhydrous dioxan. Unfortunately, however, although it was possible to conduct these reactions in this solvent, the use of liquid ammonia solutions of lithium amide for the preparation of these lithium alkynyls was still necessary, and a means of obviating this also was sought.

The possibility of employing the diacetylenylmercury compounds $(R{\cdot}C{\equiv}C)_2Hg$ in the synthesis of acetylenic compounds had always been considered attractive and appeared even more promising when it was found that such derivatives were very soluble in dioxan. These compounds are easily prepared from monoalkylacetylenes by Johnson and McEwan's method (*J. Amer. Chem. Soc.*, 1926, **48**, 469). When their solutions in dioxan were heated with lithium metal under nitrogen or in an autoclave, almost quantitative formation of the corresponding lithium alkynyls resulted, and mercury was liberated (cf. the early preparations of sodium and lithium alkyls by Schlenk and Holtz, *Ber.*, 1917, **50**, 262). In this way lithium alkynyls could be prepared without the use of either elaborate apparatus or liquid ammonia solutions of lithium amide. The method has the following advantages: (1) undesirable side-reactions, such as the formation of alkylamines, are eliminated; (2) unchanged monoalkylacetylenes can be recovered from the crude reaction products as their mercury derivatives (normal purification process), and subsequently used again; and (3) the monoalkylacetylenes can be brought into reaction in a very high degree of purity as their mercury derivatives, since these, unlike the free acetylenes, are not subject to autoxidation.

This modified method gave a 62% yield of *n*-octadec-2-yne, the intermediate *n*-heptadec-1-ynyl-lithium being prepared from di-*n*-heptadec-1-ynylmercury and treated (at 110° in an autoclave) with methyl sulphate. *n*-Octadec-4-yne (50%) and *n*-octadec-6-yne (54%) were similarly obtained from the appropriate mercury compounds and alkyl bromides under nitrogen in boiling dioxan.

Previously, the limit of application of sodium alkynyls with respect to the molecular weight of the intermediates involved had not been clearly defined. Therefore, several dialkylacetylenes of much higher molecular weight were synthesised. The yields decreased considerably with increasing molecular weight but, in view of the size of the alkyl groups involved, may still be considered practicable in comparison with those obtained by other methods. The following were synthesised: *n*-tricos-4-yne (54%, in liquid ammonia); *n*-octacos-9-yne (32%, in anhydrous dioxan); *n*-dotriacont-16-yne (34%, in dioxan by the mercury–lithium exchange reaction); and *n*-hexatriacont-17-yne (15% and 16%, in liquid ammonia and dioxan, respectively). Various modes of formation of the lithium alkynyls were employed in these syntheses.

The twelve monoalkylacetylenes required in this work, including *n*-octadec-1-yne, were prepared from sodium acetylide and the appropriate *n*-alkyl bromides in liquid ammonia. The procedures, but for two modifications, were those given by Nieuwland *et al.* (*loc. cit.*). These modifications were (1) the speedy formation of sodium acetylide in simple apparatus at −55° to −60°, at which temperature acetylene is considerably more soluble in solutions of sodium in liquid ammonia, and (2) the use of a 50% excess of sodium acetylide which minimised the formation of basic by-products. All of the $C_{>8}$ homologues were prepared in an autoclave at room temperature.

Although *n*-hexadec-1-yne had been obtained in good yield by the above method, it was also prepared from cetyl alcohol. Dehydration of the alcohol over alumina at 350° (Roberti, Minervini, and Berti, *Energia Termica*, 1941, 582; *Chem. Abs.*, 1942, **36**, 5767) yielded an impure mixture of *n*-hexadecenes which, on treatment with bromine and then with potassium hydroxide in boiling *n*-butanol, gave mixed *n*-hexadecynes containing none of the 1-isomer. Freshly prepared sodamide at 160—190° effected a 65% isomerisation of this mixture to the 1-isomer. The overall yield was of the order of 15% only.

Final purification of the liquid *n*-octadecynes was attempted by fractional distillation at low pressure in a still modelled on that described by Dixon (*J. Soc. Chem. Ind.*, 1949, **68**, 299). However, extensive decomposition occurred, mainly owing to polymerisation and oxidation caused by the long heating and presence of air in the distillation apparatus, although much polymerisation still occurred during distillation under nitrogen. Traces of *n*-octadecan-9-one were isolated from the residue after attempted fractionation of *n*-octadec-9-yne at 25 mm. in air, probably owing to vapour-phase hydration of the acetylene by atmospheric moisture, catalysed by the Nichrome-gauze packing of the still. No ketone could be detected when the distillation was attempted under dry nitrogen.

Purification by fractional crystallisation from acetone at low temperatures was satisfactory. The apparatus employed was a modification of that described by J. C. Smith (*J.*, 1939, 944). The purified hydrocarbons, pending the determination of their physical constants, were stored in evacuated ampoules.

We are indebted to Dr. H. W. Thompson, F.R.S., and Mr. D. C. McKean (Department of Physical Chemistry, Oxford University) for the determination of the infra-red absorption spectra of the *n*-octadecyne series. They report that the triple-bond stretching frequency (at 2128 cm.$^{-1}$)

was appreciably intense only in *n*-octadec-1-yne. Octadec-1-yne is readily recognised by the H–C≡ and –C≡C– stretching vibrations at 3315 and 2128 cm.$^{-1}$, characteristic of monoalkylacetylenes. The spectra of the remaining members of the series show small but definite variations in frequency and intensity in the region 1500—700 cm.$^{-1}$ which enable them to be distinguished from each other. Other bands at 2223, 1720, and 1680 cm.$^{-1}$ in certain of the samples which were left exposed to air, indicated the presence of small quantities of oxidation products, one of which was probably an α-acetylenic ketone.

These *n*-octadecynes were required as intermediates in an investigation of the *n*-octadecenes, the preparation of which will be reported later.

Experimental.

(Analyses are by Mr. F. C. Hall, and Drs. Weiler and Strauss, Oxford. M. p.s and f. p.s below −10° were determined with pentane-in-glass thermometers; those between −10° and +30° were determined with Anschütz thermometers. All m. p.s above 30°, and all b. p.s were determined with mercury-in-glass thermometers, and are uncorrected.)

Monoalkylacetylenes.—General. Monoalkylacetylenes used as intermediates were synthesised from the appropriate *n*-alkyl bromides (except in the case of *n*-hept-1-yne, where *n*-amyl chloride was employed) and sodium acetylide (50% excess) in liquid ammonia. The C_4, C_5, and C_6 homologues were prepared under atmospheric pressure at −34°, all others in an autoclave at normal temperature. The transference of the liquid ammonia reaction mixtures to the autoclave was best carried out after precooling of the autoclave with liquid air. The yields and physical constants are recorded in the Table.

		Present work.			Literature.		
	Yields, %.	M. p.	B. p., mm.	n_D^{20}.	M. p.	B. p., mm.	n_D^{20}.
Pent-1-yne	65·0	—	40·2°/763	1·3865	—	39·7°/760	1·3860
Hex-1-yne	67·2	—	70·5°/758	1·3993	—	71·0°/760	1·3990
Hept-1-yne	35·0	—	98·6°/758	1·4086	—	99·6°/760	1·4083
Oct-1-yne	65·5	—	124·5°/757	1·4168	—	126·0°/760	1·4169
Non-1-yne	79·0	—	48·5°/17	1·4224	—	151·0°/760	1·4230
Dec-1-yne	82·0	—	170·5°/761	1·4269	?	?	?
Tridec-1-yne ...	86·6	2·5°	130·0°/30	1·4374	—	—	—
Pentadec-1-yne	79·0	15·0	158·0°/30	1·4422	*	*	*
Hexadec-1-yne	86·0	14·8	144·0°/10	1·4444	15·0°	155·0°/15	—
Heptadec-1-yne	82·6	26·0	171·0°/17	1·4421 †	—	—	—
Octadec-1-yne	74·0	28·0	175—177°/13	1·4440 †	28·0	180·0°/15	—

? = No reliable data recorded. * = Ryden, Glavis, and Marvell (*J. Amer. Chem. Soc.*, 1937, **59**, 1014) give b.p. 112—113°/5 mm., n_D^{20} 1·4410, for an apparently impure specimen. † At 30°. Literature values are taken from Egloff, "Physical Constants of Hydrocarbons," Vol. I.

n-*Tridec*-1-*yne*. A rapid stream of pure dry acetylene was passed into solution of sodium (8·6 g., 0·325 g.-atom) in liquid ammonia (500 c.c.), the solution being kept at −55° to −60° by means of ethanol–solid carbon dioxide. A stainless-steel autoclave (750 c.c.) was meanwhile chilled by the addition of liquid air. *n*-Undecyl bromide (59 g., 0·25 mole; b. p. 132°/10 mm.; n_D^{20} 1·4570) and the sodium acetylide solution were added to the autoclave, which was immediately sealed. The reaction was allowed to proceed at room-temperature for 24 hours, the autoclave being agitated by means of an eccentric. After venting of the ammonia *via* the needle-valve, crushed ice (300 g.) was added to the product to decompose any unchanged sodium acetylide. The crude hydrocarbon, in ether, was repeatedly washed with dilute hydrochloric acid (6%) to remove basic contaminants, before being dried (Na_2SO_4). Removal of the ether, followed by a preliminary distillation, yielded *n*-tridec-1-yne (42 g.) as a colourless liquid, fractionation (Dufton spiral column) of which gave the pure *hydrocarbon* (39 g., 86·6%) (Found: C, 86·5; H, 13·4. $C_{13}H_{24}$ requires C, 86·7; H, 13·6%). The derived mercury compound crystallised from benzene as colourless needles of m. p. 87—88°.

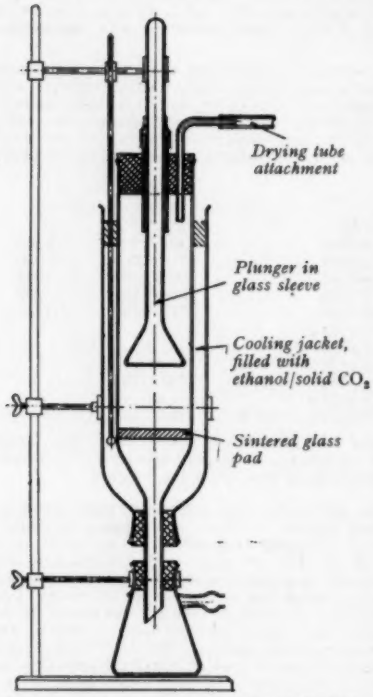
n-*Heptadec*-1-*yne*. *n*-Pentadecyl bromide (b. p. 184°/15 mm., f. p. 17·9°, n_D^{20}, 1·4612) was prepared from the alcohol in 81·5% yield by the method of Reid, Ruhoff, and Burnett (*Org. Synth.*, Coll. Vol. II, 1944, p. 246). The bromide (146 g., 0·502 mole), on treatment with sodium acetylide (from sodium, 17·5 g., 0·762 g.-atom) as above, yielded crude *n*-heptadec-1-yne as a golden-yellow oil which solidified when kept. Crystallisation from ethanol, following decolorisation with charcoal, gave the pure *hydrocarbon* (97·5 g., 82·6%) as large lustrous plates (Found: C, 86·6; H, 13·4. $C_{17}H_{32}$ requires C, 86·4; H, 13·6%).

n-*Octadecynes*.—n-*Octadec*-9-*yne*. Interaction of *n*-octyl bromide (77 g., 0·4 mole), lithium acetylide, and lithium amide (both from lithium, 1·4 g., 0·2 g.-atom, in 250 c.c. of liquid ammonia), in an autoclave, followed by fractional distillation of the crude product obtained after 24 hours, yielded *n*-octadec-9-yne (30 g., 60%) and *n*-dec-1-yne (11·4 g., 41%). The hydrocarbon, after purification by fractional crystallisation from acetone at low temperature, had b. p. 179°/17 mm., m. p. −0·4°, f. p. −0·3°, n_D^{20} 1·4503, n_D^{25} 1·4458, d_4^{20} 0·8040, and d_4^{25} 0·7950 (the technique of low-temperature crystallisation from acetone is described later) (Found: C, 86·4; H, 13·5. Calc. for $C_{18}H_{34}$: C, 86·4; H, 13·6%). Bried and Hennion (*loc. cit.*) record b. p. 163—164°/7 mm. and n_D^{25} 1·4488.

n-*Octadec*-8-*yne*. *n*-Nonyl bromide (27 g., 0·13 mole) and *n*-non-1-yne (17 g., 0·137 mole) in liquid ammonia (500 c.c.) containing lithium amide (from lithium 1 g., 0·144 g.-atom) similarly gave, after fractionation at 18 mm., *n*-non-1-yne (2 g.; b. p. 48°) and n-*octadec*-8-*yne* (23 g., 67%), which, after

low-temperature crystallisation, had b. p. 167—168°/11 mm., m. p. −2·5°, f. p. −2·4°, n_D^{20} 1·4505, n_D^{25} 1·4451, d_4^{20} 0·8054, and d_4^{25} 0·7957 (Found: C, 86·7; H, 13·3. $C_{18}H_{34}$ requires C, 86·4; H, 13·6%).

Similarly were prepared: n-*octadec-7-yne*, (19 g., 76%), b. p. 169°/11 mm., m. p. −9·2°, f. p. −9·0°, n_D^{20} 1·4504, n_D^{25} 1·4447, d_4^{20} 0·8043, and d_4^{25} 0·7938 (Found: C, 86·5; H, 13·5. $C_{18}H_{34}$ requires C, 86·4; H, 13·6%), from *n*-oct-1-yne (11 g., 0·1 mole), *n*-decyl bromide (23 g., 0·104 mole) and lithium amide (from lithium 0·8 g., 0·115 g.-atom), in liquid ammonia (500 c.c.); n-*octadec-6-yne* (38 g., 76%), b. p. 164°/9 mm., m. p. −1·4°, f. p. −1·4°, n_D^{20} 1·4508, n_D^{25} 1·4451, d_4^{20} 0·8089, and d_4^{25} 0·7984 (Found: C, 86·6; H, 13·6%), from *n*-undecyl bromide (47 g., 0·2 mole), *n*-hept-1-yne (19·5 g., 0·203 mole) and lithium amide (from lithium 1·6 g., 0·23 g.-atom) in liquid ammonia (500 c.c.); n-*octadec-5-yne* (26 g., 52%), b. p. 168—169°/11 mm., m. p. −7·8°, f. p. −7·8°, n_D^{20} 1·4499, n_D^{25} 1·4442, d_4^{20} 0·8036, and d_4^{25} 0·7939 (Found: C, 88·6; H, 13·8%), from *n*-dodecyl bromide (50 g., 0·2 mole) and *n*-hex-1-yne (17 g., 0·207 mole) in liquid ammonia (500 c.c.) containing the requisite amount of lithium amide (from lithium 1·6 g., 0·23 g.-atom); n-*octadec-4-yne* (31 g., 62%), b. p. 169—170°/12 mm., m. p. 3·7°, f. p. 3·8°, n_D^{20} 1·4510, n_D^{25} 1·4453, d_4^{20} 0·8078, d_4^{25} 0·7973 (Found: C, 86·4; H, 13·5%), by reaction, in liquid ammonia (500 c.c.) containing lithium amide (from lithium 1·6 g., 0·23 g.-atom), between *n*-tridecyl bromide (53 g., 0·2 mole) and *n*-pent-1-yne (14 g., 0·206 mole); and n-*octadec-3-yne*, b. p. 193·5°/25 mm., m. p. 2·4°, f. p. 2·2°, n_D^{20} 1·4492, n_D^{25} 1·4436, d_4^{20} 0·8049, and d_4^{25} 0·7944 (78%, 39 g.) (Found: C, 86·3; H, 13·5%), from but-1-yne (16 g., 0·296 mole; weighed in a small Dewar flask) and *n*-tetradecyl bromide (55·4 g., 0·2 mole) in a liquid ammonia solution of lithium amide (from lithium 1·6 g., 0·23 g.-atom).



Low-temperature crystallisation apparatus.

n-*Octadec-2-yne*.—Di-*n*-heptadec-1-ynylmercury was obtained by adding *n*-heptadec-1-yne (50 g., 0·212 mole) in ethanol (1 l.) to a mechanically stirred solution of alkaline mercuric iodide (cf. Johnson and McEwan, *J. Amer. Chem. Soc.*, 1926, **48**, 469). The reagent was prepared by adding 10% aqueous sodium hydroxide (125 c.c.) to mercuric chloride (66 g.) and potassium iodide (163 g.) in water (163 c.c.). The white precipitate of the mercury compound was well washed with 50% ethanol. After being dried on the water-bath, this material crystallised from benzene (400 c.c.) as sparkling white rectangular plates, m. p. 99° (66·1 g., 93·2%).

To the mercury compound (66·1 g., 0·099 mole) in dry dioxan (450 c.c.) in a dry stainless-steel autoclave (750-c.c. capacity), lithium (1·5 g., 0·216 g.-atom) which had been beaten to a fine foil under liquid paraffin was then added, and the autoclave immediately sealed. Heating at 110°, and agitation, were carried out for 12 hours. Methyl sulphate (31·5 g., 0·25 mole) was then added to the resultant milky suspension, and the autoclave was again heated to 110° and shaken for 30 hours. The resulting mixture, which contained a large amount of a light-yellow solid, was poured on crushed ice (500 g.). No evolution of hydrogen was observed (absence of unchanged lithium acetylide). Approx. 18 g. (*ca.* 90%) of mercury were recovered, which indicated that the metal exchange reaction had proceeded almost quantitatively. The product was extracted from the aqueous dioxan with ether. After washing and drying of this extract, the ether was removed. The crude product—a brown solid at room temperature—was distilled. The distillate (b. p. 182—186°/26 mm.; 38 g., 76%) contained traces of mercury and volatile mercury salts. It gave a slight precipitate with ethanolic silver nitrate. The *n*-heptadec-1-yne was removed almost completely by treating the crude product with alkaline mercuric iodide as described above. Precipitated di-*n*-heptadec-1-ynylmercury was washed free from adsorbed *n*-octadec-2-yne with light petroleum (b. p. 60—80°), in which the diacetylenyl compound is but sparingly soluble. The diluted mother-liquors and washes were extracted thrice with more light petroleum, and the combined extracts were washed until neutral before drying (Na_2SO_4). After removal of the light petroleum, the now almost pure *n*-octadec-2-yne (34 g.) was distilled (b. p. 178—180°/20 mm.). The product then still contained traces of *n*-heptadec-1-yne and was finally purified by crystallisation from methanol.

n-Octadec-2-yne, free from *n*-heptadec-1-yne, was obtained as lustrous white plates (30·5 g., 61·8%), b. p. 186°/22 mm., m. p. 30—30·5°, n_D^{20} 1·4488, n_D^{25} 1·4467, and d_4^{25} 0·7980 (Krafft, *Ber.*, 1884, **17**, 1372, gives b. p. 184°/15 mm., m. p. 30°, and d_4^{20} 0·8016) (Found: C, 86·05; H, 13·6%).

Fractional Distillation of n-*Octadec-9-yne*.—The still employed was that described by Dixon (*J. Soc. Chem. Ind.*, 1949, **68**, 299). The hydrocarbon distilled constantly at 191·8°/25 mm. During the distillation the liquid progressively darkened from colourless to a dark red, and distillation suddenly ceased when about half of the material had been collected. The dark residue could not be distilled under 0·01 mm., and its solution in light petroleum exhibited an intense green fluorescence. Chromatography on alumina and silica columns failed to separate any recognisable fraction.

A white crystalline compound (trace) was found adhering to the column packing and the lower part of the still-head, and was extracted with boiling acetone. Crystallisation from methanol yielded clusters of small plates (*ca.* 20 mg.), m. p. 47·5—48° (Found: C, 80·5; H, 13·5. Calc. for $C_{18}H_{36}O$: C, 80·6; H, 13·4%). No depression of m. p. occurred on admixture with an authentic specimen of *n*-octadecan-9-one, and the infra-red spectra of the specimens were identical. No ketonic material was detected when the distillation was done in an atmosphere of dry nitrogen. The ketone for comparison was obtained in 83% yield by heating *n*-octadec-9-yne (3 g.; Thomas, Campbell, and Hennion, *J. Amer. Chem. Soc.*, 1938, **60**, 718) in acetone (125 c.c.)—water (10 c.c.) in the presence of 1 g. each of concentrated sulphuric acid and mercuric sulphate for 12 hours under reflux, and formed small white plates (from methanol), m. p. 48° (Found: C, 80·4; H, 13·25%).

Low-temperature Crystallisation of the Liquid n-*Octadecynes.*—Ethereal solutions of the hydrocarbons were washed with dilute aqueous solutions of the usual reagents, to remove possible oxidation products. The recovered hydrocarbons were distilled through a small Vigreux column, and the constant-boiling fractions collected. These samples were then dissolved in acetone (*ca.* 20 g. in 100 c.c. of solvent). The hydrocarbons were crystallised at low temperature, by means of the apparatus illustrated.

The solution of the hydrocarbon, contained in a glass-stoppered conical flask, was slowly chilled in a bath of ethanol by the addition of small portions of solid carbon dioxide. Crystallisation, in the case of *n*-octadec-9-yne, began at −30°, and the temperature was further lowered to −50°. Meanwhile the cooling jacket of the filtration apparatus was cooled to −45°, also by the addition of solid carbon dioxide. The mixture of solid and mother-liquor was then speedily transferred to the funnel, and the temperature kept at −45° for 15 minutes. The solvent was withdrawn by means of the water-pump, and the solid washed with acetone chilled to −50°. After three washes, each with 75 c.c. of acetone, the apparatus was left to regain room temperature. The liquid hydrocarbon was then collected in a clean flask and immediately distilled.

n-*Tricos*-4-*yne.*—The reaction between *n*-octadecyl bromide (33·5 g., 0·1 mole) and *n*-pent-1-yne (7 g., 0·103 mole) in liquid ammonia (500 c.c.) containing lithium amide (from lithium 0·7 g., 0·1 g.-atom), in an autoclave at room temperature for 48 hours, yielded the crude hydrocarbon, contaminated mainly with unchanged bromide. The product, dissolved in ether (250 c.c.), was purified by shaking it with liquid ammonia for 24 hours at room temperature in an autoclave. The recovered material was free from alkyl bromide. Pure n-*tricos*-4-*yne* (17·6 g., 54%) crystallised from methanol–ethanol as clusters of small plates, m. p. 24°, b. p. 232—233°/15 mm., and n_D^{25} 1·4535 (Found: C, 86·3; H, 13·6. $C_{23}H_{44}$ requires C, 86·2; H, 13·7%).

n-*Octacos*-9-*yne.*—A suspension of lithium amide (from lithium 0·4 g., 0·058 g.-atom) in dioxan (150 c.c.) was prepared by adding anhydrous dioxan to a liquid-ammonia solution of lithium amide, and heating the whole under reflux under anhydrous conditions until all the ammonia was dispelled. This suspension, together with *n*-octadecyl bromide (16·7 g., 0·05 mole) and *n*-dec-1-yne (6·9 g., 0·05 mole), was added immediately to a tilting autoclave of 250-c.c. capacity, and shaken at 110° for 15 hours. The product was isolated in the usual manner, and the part boiling below 200°/15 mm. was discarded, being mainly unchanged bromide. The residue, a brown solid, was crystallised twice from glacial acetic acid (charcoal), yielding n-*octacos*-9-*yne* (6·25 g., 32%) as large glistening white plates, m. p. 36° (Found: C, 86·2; H, 13·7. $C_{28}H_{54}$ requires C, 86·15; H, 13·85%).

n-*Dotriacont*-16-*yne.*—A solution of di-*n*-heptadec-1-ynylmercury (13·4 g., 0·02 mole) in boiling anhydrous dioxan (150 c.c.) was treated with excess of lithium (0·05 g., 0·072 g.-atom) under nitrogen. When the exchange reaction was complete (*ca.* 30 minutes), the solution of the lithium derivative was transferred, *via* a " bridge " of glass tubing incorporating a glass-wool filter, into a second all-glass apparatus by means of a pressure of nitrogen. To this solution was added *n*-pentadecyl bromide (11·64 g., 0·04 mole) in dioxan (100 c.c.), and the whole heated under reflux in a nitrogen atmosphere for 16 hours. The product was then isolated in the usual manner, and that part of b. p. higher than 170°/14 mm., a brown solid, was crystallised twice (charcoal) from ethanol. n-*Dotriacont*-16-*yne* (6 g., 34%) was obtained as small nacreous plates, m. p. 58° (Found: C, 85·9; H, 13·8. $C_{32}H_{62}$ requires C, 86·1; H, 13·9%). Catalytic hydrogenation (Raney nickel) of the acetylene in ethyl acetate gave the known *n*-dotriacontane (m. p. 70°; lit., m. p. 70°) (Found: C, 85·0; H, 15·0. Calc. for $C_{32}H_{66}$: C, 85·3; H, 14·7%).

n-*Hexatriacont*-17-*yne.*—(a) *In liquid ammonia.* A solution of lithium amide (from lithium 0·35 g., 0·05 g.-atom) in liquid ammonia (200 c.c.) was heated in an autoclave for 20 hours with a light petroleum (b. p. 40—60°; 200 c.c.) solution of *n*-octadec-1-yne (12·5 g., 0·05 mole) and *n*-octadecyl bromide (16·7 g., 0·05 mole). The product of b. p. >208°/11 mm. crystallised from ethanol (charcoal) as a white solid (4 g.) of no definite crystalline form, but tending to needles, having m. p. 51—54°. Recrystallisation from ethanol and glacial acetic acid in turn gave n-*hexatriacont*-17-*yne* as small nacreous plates, m. p. 53—53·5° (15%, 3·75 g.) (Found: C, 86·2; H, 13·8. $C_{36}H_{70}$ requires C, 86·1; H, 13·9%).

(b) *In anhydrous dioxan.* In an attempt to increase the yield, the synthesis was repeated, employing the mercury–lithium exchange reaction in dioxan for formation of the lithium derivative. *n*-Hexatriacont-17-yne was obtained in only 16% yield (1·75 g.) from *n*-octadec-1-ynyl-lithium (from di-*n*-octadec-1-ynylmercury, 9·3 g.) and *n*-octadecyl bromide (8·9 g.) under nitrogen in dioxan (150 c.c.) for 11 hours. The procedure was that described for *n*-dotriacont-16-yne.

The authors thank Professor Sir Robert Robinson, O.M., F.R.S., for his interest in this work, and the Anglo-Iranian Oil Company Ltd. for financial support and a research grant to one of them (P. F. M. P.).

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[*Received, December 15th,* 1950.]

201. *The Reduction of Allylamines with Sodium in Liquid Ammonia.*

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The reduction by sodium in liquid ammonia in the presence of alcohol of eight tertiary amines containing a double bond in the allyl position to the nitrogen has been investigated. In no case did hydrogenolytic fission, such as occurs in the reduction of allyl ethers and alcohols, take place, but with three amines, *N*-allyl- and -methallyl-piperidine and diethylmethallylamine, reduction occurred to give the saturated compound. *N*-Crotyl-, -2-*tert.*-butylallyl-, -1-*cyclo*hex-2′-enyl-, -benzyl-, and -2 : 3 : 4 : 5-tetrahydrobenzyl-piperidine were unaffected by sodium in liquid ammonia. The above amines and the corresponding saturated derivatives have been characterised.

THE reductive fission by sodium in liquid ammonia of allyl alcohols has been well investigated, but the similar reduction of allylamines has been little studied. In the case of the oxygen compounds it seems possible to make the generalisation that, if in the system $>\overset{1}{C}=\overset{2}{C}-\overset{3}{C}-O-R$ either of the atoms C_1 or C_3 carries H_2 or PhH, then reduction will take place with fission of the C_3–O link (see Birch, *Quart. Reviews*, 1950, **4**, 69). In no case has reduction of the double bond been reported unless this is conjugated with another olefinic link or with a phenyl substituent. The fission of allylamines under the action of potassium or sodium has been reported on two occasions; by Clayson (unpublished work, see Birch, *loc. cit.*) who has observed the fission of the heterocyclic ring in laudanosine, and by Clemo and King (*J.*, 1948, 1661) to account for the uptake of six atoms of hydrogen in the sodium–ammonia reduction of strychnine. Strychnine contains the group $-O-CH_2-CH=\overset{|}{C}-CH_2-N\lessdot$, and it was to confirm the possibility of hydrogenolytic fission in simple aliphatic tertiary allylamines that this work was carried out.

The first amine to be investigated was *N*-allylpiperidine prepared by reaction of allyl bromide with two equivalents of piperidine in benzene (Menschutkin, *J. Russ. Phys. Chem. Soc.*, 1899, **31**, 43; *Chem. Zentr.*, 1899, I, 1066). The purity of the product was checked by analysis and by quantitative catalytic hydrogenation. Reduction was carried out by using an excess of sodium in the presence of methanol as a proton source. All attempts to isolate piperidine or to detect its presence in the reaction mixture were unsuccessful, the product being a tertiary amine, characterised as the picrate and methiodide, and identified as *N*-propylpiperidine by comparison of these derivatives with the corresponding derivatives obtained from *N*-propylpiperidine prepared from piperidine and propyl iodide and by catalytic reduction of allylpiperidine. When only two equivalents of sodium were used in this reduction catalytic hydrogenation showed the presence of 45% of unsaturated material in the crude product, but when 5—6 equivalents of sodium were used less than 15% of the starting material remained unreduced. This result was very surprising, being so far as we know the only reported case of chemical reduction of a double bond unconjugated with another unsaturated centre.

To determine the influence of substituents on the course of the reduction the following amines were prepared (with the exception of the diethylamine derivative, in the preparation of which no solvent was used, by the standard procedure used for allylpiperidine) and subjected to the action of sodium in ammonia: diethylmethallylamine, *N*-methallyl-, *N*-crotyl-, *N*-*cyclo*hex-2-enyl-, *N*-2-*tert.*-butylallyl-, *N*-benzyl-, and *N*-2 : 3 : 4 : 5-tetrahydrobenzyl-piperidine.

A standard procedure was employed for the reduction of the amines and for the working up of the reaction mixture. In each case the crude product was isolated with ether and distilled with no attempt at fractionation. A portion of the total distillate was then subjected to quantitative catalytic reduction (not carried out with *N*-benzylpiperidine) and the remainder converted into the picrate and methiodide. Picrates and methiodides of the unsaturated amines and of the corresponding saturated compounds, made by catalytic reduction of the olefinic amine and sometimes also from the appropriate saturated halide, were also prepared for the purpose of comparison. Throughout the whole series we found it an invariable rule that the same derivative of both saturated and unsaturated amines having the same carbon skeleton did not show a depression of melting point when mixed. However, the actual melting points of the saturated and unsaturated compounds were usually very different and the routine

quantitative hydrogenation carried out did not allow of any confusion between reduced and unreduced material.

Of the amines investigated only diethylmethallylamine, and allyl- and methallyl-piperidine were reduced under the conditions employed. With the remaining amines catalytic reduction of the product from the treatment with sodium in ammonia showed the presence of 98—101% of unsaturated material, *i.e.* a value indistinguishable from that obtained for the pure unsaturated compound. The non-reduction of *N*-crotylpiperidine, bearing so close a relationship to *N*-methallylpiperidine, would seem to indicate that reduction under the conditions investigated is confined to terminal double bonds. The failure of *tert.*-butylallylpiperidine to undergo reduction may be due either to the inductive effect of the *tert.*-butyl substituent or to steric effects.

Experimental.

Preparation of Amines.—The unsaturated bases and certain of the saturated bases were prepared by interaction of the appropriate halide with two equivalents of base in benzene as solvent. The halides used were methallyl chloride (commercial), crotyl bromide (Charon, *Ann. Chim. Phys.*, 1899, **17**, 233), 3-bromo*cyclo*hexene (Ziegler *et al.*, *Annalen*, 1942, **551**, 80), 2-*tert.*-butylallyl bromide [from 2-*tert.*-butylpropene (Edgar, Calingaert, and Marker, *J. Amer. Chem. Soc.*, 1929, **51**, 1483), and *N*-bromosuccinimide], benzyl chloride, 2-bromo-1-methylene*cyclo*hexane (Mousseron, Winternitz, and Jacquier, *Compt. rend.*, 1947, 1062), and 1-bromomethyl*cyclo*hexene. The last was prepared, in small yield, by the action of hydrobromic acid on the corresponding alcohol, which was readily obtained by lithium aluminium hydride reduction of *cyclo*hexene-1-carboxylic acid, prepared by acid (70% sulphuric acid) hydrolysis of the appropriate cyanide (Ruzicka and Brugger, *Helv. Chim. Acta*, 1926, **9**, 399). From the last two bromides only one tertiary amine was obtained, reaction of piperidine with 2-bromo-1-methylene*cyclo*hexane presumably being accompanied by an allylic shift.

With the unsaturated halides the initial reaction with the amine was vigorous and external cooling was usually required. When the reaction had subsided the mixture was heated on the steam-bath for 2 hours and then cooled, and the base hydrohalide removed by filtration and well washed with benzene. The combined filtrate and washings were finally distilled giving the amine. The bases were characterised as the picrates, prepared in ethanol and crystallised from aqueous ethanol, and as the methiodides, prepared in the absence of solvent and purified from acetone–ethyl acetate. *tert.*-Butylallylpiperidine methiodide had an unsatisfactory m. p., and the hydrogen oxalate was therefore also prepared.

Catalytic Reduction of the Unsaturated Bases.—Both analytical and preparative reductions were carried out quantitatively at room temperature and pressure, Adams's platinic oxide being used as catalyst and ethanol containing just more than one equivalent of hydrochloric acid as solvent. Reduction was rapid. In preparative reductions the products were isolated by evaporation of the solvent, treatment of the residue with aqueous sodium hydroxide (40%), and extraction of the liberated oil with ether followed by distillation. Yields of distilled base were in the range 80—90%, varying slightly with the solubility of the amine in aqueous sodium hydroxide. For characterisation picrates and methiodides were prepared.

Reduction of the Bases with Sodium in Ammonia.—(*a*) *N*-Allylpiperidine (Found: C, 76·6; H, 11·8. Calc. for $C_8H_{15}N$: C, 76·8; H, 12·0%) (1 g.) and methanol (1 c.c.) in ammonia (80 c.c.) in an unsilvered Dewar vessel were treated with successive small portions of sodium, with stirring between each addition until the blue colour was discharged. When 2 g. of sodium had been added the solution was poured into a beaker and the ammonia and methanol allowed to evaporate. Water (15 c.c.) was added to the solid residue, and the liberated oil taken up in ether and distilled, giving an oil (0·75 g., 75%), b. p. 148—150°, which on catalytic reduction showed the presence of 0·1 double bond per molecule. The picrate, m. p. 112° (Auerbach and Wolffenstein, *Ber.*, 1899, **32**, 2511, give m. p. 121°; Evans, *J.*, 1897; 524, gives m. p. 108°) (Found: C, 47·0; H, 5·5. Calc. for $C_4H_{17}N,C_6H_3O_7N_3$: C, 47·2; H, 5·6%), and methiodide, m. p. 185° (von Braun, *Ber.*, 1909, **42**, 2534, gives m. p. 181—182°) (Found: N, 4·8. Calc. for $C_9H_{18}NI$: N, 5·2%), were identical in appearance and m. p. with the derivatives obtained from propylpiperidine made both by catalytic reduction of allylpiperidine and by the reaction between propyl iodide and piperidine. The base hydrochloride was prepared from the picrate and purified by sublimation; it had m. p. 227°. Auerbach and Wolffenstein (*loc. cit.*) gave m. p. 212° for propylpiperidine hydrochloride, but an authentic specimen prepared by us, after crystallisation from acetone, had m. p. 226—227°.

(*b*) *N*-Methallylpiperidine and diethylmethallylamine were reduced as in (*a*). The crude product (72%) from the piperidine showed 0·15 double bond per molecule, and that from the diethylamine derivative (51%, low yield probably due to the greater solubility of this base in alkali) showed 0·13 double bond per molecule. Picrates and methiodides were prepared and corresponded with those obtained from the authentic saturated amines.

(*c*) The remaining unsaturated amines were entirely unchanged on attempted reduction under these conditions, or when more methanol and/or more sodium was employed. The substitution of ammonium chloride for methanol as the proton source was equally ineffective. The crude bases after attempted reduction gave on catalytic reduction 0·98—1·01 double bonds per molecule. (Benzylpiperidine was not subjected to catalytic reduction.)

Details of the amines and salts prepared in connection with this work are given in the table.

3-*Bromo*-2-tert.-*butylpropene.*—2-*tert.*-Butylpropene (Edgar *et al.*, *loc. cit.*) (9 g., 1 mol.) and *N*-

bromosuccinimide (16·3 g., 1 mol.) in carbon tetrachloride (100 c.c.) were boiled under reflux for 4 hours. The solid was removed and the filtrate distilled, giving a fuming, cloudy liquid, b. p. 160—190°, which

Compound.	Yield,[a] %	B. p. or m. p.	Cryst.[b] form.	Formula.	Found, %. C.	H.	N.	Required, %. C.	H.	N.
N-Allylpiperidine	67	148—151°	—	$C_8H_{15}N$	—	—	—	—	—	—
picrate		85	A	$C_{14}H_{18}O_7N_4$	—	—	15·7	—	—	15·8
methiodide		oily	—	$C_9H_{18}NI$	—	—	—	—	—	—
N-*Methallylpiperidine*	71	164	—	$C_9H_{17}N$	77·4	12·2	—	77·7	12·2	—
picrate		117—118	B	$C_{15}H_{20}O_7N_4$	49·2	5·5	15·5	48·9	5·4	15·2
methiodide		oily	—	$C_{10}H_{20}NI$	—	—	—	—	—	—
Diethylmethallylamine[c]	52	129	—	$C_8H_{17}N$	—	—	10·8	—	—	11·0
picrate		91—92	E	$C_{14}H_{20}O_7N_4$	47·1	5·3	—	47·2	5·6	—
methiodide		171	C	$C_9H_{20}NI$	40·1	7·4	—	40·2	7·4	—
N-*Crotylpiperidine*[d]	74	61/11 mm.	—	$C_9H_{17}N$	78·0	12·2	—	77·7	12·2	—
picrate		98—99	A	$C_{15}H_{20}O_7N_4$	49·4	5·3	—	48·9	5·4	—
methiodide		119	C	$C_{10}H_{20}NI$	43·1	7·2	—	42·7	7·1	—
N-cyclo*Hex*-2-*enylpiperidine*	88	105/10 mm.	—	$C_{11}H_{19}N$	80·3	11·2	—	80·3	11·5	—
picrate		108—109	A	$C_{17}H_{22}O_7N_4$	52·1	6·0	—	51·8	5·6	—
methiodide		160	D	$C_{12}H_{22}NI$	46·5	6·8	—	46·9	7·2	—
N-2-tert.-*Butylallylpiperidine*	71	95/12 mm.	—	$C_{12}H_{23}N$	79·9	12·6	—	79·6	12·7	—
picrate		104 (undried) 132 (dried) at 100°/12 mm.	A	$C_{18}H_{26}O_7N_4$	(on dried sample)		13·8	—	—	13·7
methiodide		148—155	D	$C_{13}H_{26}NI$	—	—	4·5	—	—	4·3
hydrogen oxalate		155	E	$C_{14}H_{25}O_4N$	—	—	5·0	—	—	5·2
N-2 : 3 : 4 : 5-*Tetrahydrobenzylpiperidine*	69	107/12 mm.	—	$C_{12}H_{21}N$	—	—	7·6	—	—	7·8
picrate		156	B	$C_{18}H_{24}O_7N_4$	52·7	6·1	—	52·9	5·9	—
methiodide		170	A	$C_{13}H_{24}NI$	48·6	7·6	—	48·6	7·5	—
N-Benzylpiperidine[e]	78	115/13 mm.	—	$C_{12}H_{17}N$	—	—	—	—	—	—
picrate		178—179	F	$C_{18}H_{20}O_7N_4$	—	—	14·2	—	—	13·9
*N-iso*Butylpiperidine[f]	62	161—163	—	$C_9H_{19}N$	—	—	—	—	—	—
picrate		144—145	D	$C_{15}H_{22}O_7N_4$	—	—	15·3	—	—	14·9
methiodide		197—198	D	$C_{10}H_{22}NI$	42·5	7·9	—	42·4	7·8	—
N-iso*Butyldiethylamine*	—	132	—	$C_8H_{19}N$	—	—	10·4	—	—	10·8
picrate		87—88	B	$C_{14}H_{22}O_7N_4$	47·3	6·2	15·5	46·8	6·15	15·3
methiodide		195	D	$C_9H_{22}NI$	40·1	8·4	—	39·9	8·1	—
N-2-tert.-*Butylpropylpiperidine*	—	95/10 mm.	—	$C_{12}H_{25}N$	78·3	13·7	—	78·6	13·7	—
picrate		135	B	$C_{18}H_{28}O_7N_4$	—	—	13·5	—	—	13·6
hydrogen oxalate		156	E	$C_{14}H_{27}O_4N$	—	—	5·3	—	—	5·1
N-cyclo*Hexylmethylpiperidine*	—	110/11 mm.	—	$C_{12}H_{23}N$	—	—	7·5	—	—	7·7
picrate		148—149	F	$C_{18}H_{26}O_7N_4$	53·2	6·7	—	52·7	6·4	—
methiodide		223—224	D	$C_{13}H_{26}NI$	47·8	8·1	—	48·3	8·05	—

(*a*) Refers to preparation from base and halide. (*b*) A = leaflets, B = prisms, C = tablets, D = needles, E = plates, F = fern-like clusters. (*c*) Made without solvent, reaction time 4 hours. (*d*) Mannich and Mangotte (*Ber.*, 1935, **68**, 273) describe a compound probably having this structure as its b. p. is 59—61°/12 mm. (picrate, m. p. 91°), no analyses were given. (*e*) Clarke (*J.*, 1912, 1807) gives b. p. 119°/13 mm. (*f*) Drake and McElvain (*J. Amer. Chem. Soc.*, 1933, **55**, 1156) give b. p. 160—161°.

was dried ($CaCl_2$) and redistilled under slightly reduced pressure; the pure *bromide* (6·5 g., 40%) had b. p. 140—145°/500 mm. (Found: Br, 44·6. $C_7H_{13}Br$ requires Br, 45·1%).

I express my thanks to Professor G. R. Clemo, F.R.S., in whose laboratory much of this work was carried out, for his help and encouragement.

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[*Received, December 18th*, 1950.]

202. *Steroids and Related Compounds. Part XII. Some Heterocyclic Derivatives.*

By H. Antaki and V. Petrow.

Quinolino-, indolo-, pyrrolo-, thiazolo-, and triazafluoreno-steroids have been prepared for biological study. All the compounds obtained proved sparingly soluble with the exception of (II; R = NH_2), which failed to show appreciable activity against a variety of organisms.

The preparation of basic derivatives of steroids for biological study has previously been recorded (cf. Haslewood, *Biochem. J.*, 1941, **35**, 1307; Barber, Dible, and Haslewood, *ibid.*, 1943, **37**, vi; Barnett, Ryman, and Smith, *J.*, 1946, 524, 528; James, Smith, Stacey, and Webb, *J.*, 1946, 665; Stacey and Webb, *Proc. Roy. Soc.*, 1947, *B*, **134**, 523, 538; Jones, Webb, and Smith, *J.*, 1949, 2164). Extension of this work to heterocyclic compounds, however, has not hitherto been described in the literature, in spite of the fact that some naturally occurring products of this type show interesting biological properties. Thus (i) the *Solanum* alkaloids β-dihydrosolasodine and tetrahydrosolasodine antagonise the positive chronotropic action of adrenaline in the anæsthetised dog (Krayer and Briggs, *Brit. J. Pharmacol.*, 1950, **5**, 118), (ii) the steroidal bases present in *Veratrum viride* appear to function as hypotensive agents in cases of essential hypertension (Wilkins, Stanton, and Freis, *Proc. Soc. Exp. Biol.*, 1949, **72**, 302), and (iii) conessine shows marked amœbicidal activity. Before considering the synthesis of such compounds, however, it seemed desirable to determine the limitations imposed by the steroidal ring system on established procedures for the preparation of the quinoline, pyrrole, indole, thiazole, and triazafluorene ring systems.

(A = ·CHMe·$[CH_2]_3$·Pr^i.) (B = ·CHMe·CH_2·CH_2·CO_2H.)

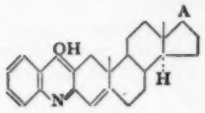
(I; R′ = A.) (I*a*; R′ = B.) (II; R′ = A.) (II*a*; R′ = B.)

Borsche and Frank (*Ber.*, 1924, **57**, 1373) had previously recorded the condensation of 3 : 12-diketo- and of 3 : 7 : 12-triketo-cholanic acid with *o*-aminobenzaldehyde and with isatin, obtaining thereby the corresponding quinolino-derivatives, but they failed to comment on their biological activity. We now find that the reaction with *o*-aminobenzaldehyde may be extended to cholestan-3-one (I) and to 3-keto*allo*cholanic acid (I*a*), to give the corresponding quinolino-derivatives in good yield. Although both linear and angular formulations are possible for these compounds, the linear structures (II; R = H) and (II*a*; R = H), respectively, are preferred in view of the established reactivity of the $C_{(2)}$ methylene group in ketones of this type (cf. Butenandt and Wolff, *Ber.*, 1935, **68**, 2091; Rosenheim and Stiller, *J.*, 1938, 353; Windaus and Kuhr, *Annalen*, 1937, **532**, 52). Unfortunately both these compounds proved too insoluble for biological study, and we had perforce to turn our attention to the synthesis of basically-substituted analogues.

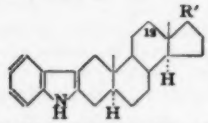
By heating cholestan-3-one (I) with anthranilic acid, 4′-hydroxyquinolino(3′ : 2′-2 : 3)-cholest-2-ene (II; R = OH) was readily obtained in excellent yield. With phosphorus pentachloride in phosphorus oxychloride this gave the corresponding 4′-chloro-compound (II; R = Cl), converted in *p*-cresol at 200° by gaseous ammonia into 4′-aminoquinolino(3′ : 2′-2 : 3)-cholest-2-ene (II; R = NH_2) (cf. Albert and Gledhill, *J. Soc. Chem. Ind.*, 1945, **64**, 169), and into the 4′-phenoxy-analogue by phenol at 130°. The action of anthranilic acid on cholest-4-en-3-one, however, appeared to follow a modified pattern. The product, it is true, gave analytical figures in good agreement with those for a 4′-hydroxyquinolino(3′ : 2′-2 : 3)cholesta-2 : 4-diene (III), but attempts at its conversion into the 4′-chloro-derivative failed. The formulation (III) assigned to this compound must, therefore, be accepted with reserve. Methyl 3-keto*allo*-cholanate, in contrast, gave methyl 4′-hydroxyquinolino(3′ : 2′-2 : 3)*allo*chol-2-enate, readily transformed into the 4′-chloro-acid (II*a*; R = Cl). Conversion of the latter product into the 4′-amino-acid (II*a*; R = NH_2), however, gave low yields. We were thus precluded from attempting a Curtius degradation.

Indolo-steroids were first described by Dorée (*J.*, 1909, 653), who prepared the " tetrahydro-

carbazole derivative from coprostan-3-one " by treating the latter with phenylhydrazine in acetic acid. Extending these observations to cholestan-3-one, Dorée and Petrow (*J.*, 1935, 1391) obtained a compound to which they assigned the formulation of an indolo(2′ : 3′ : 3 : 4)cholestane.



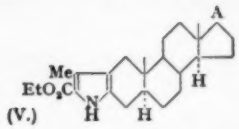
(III.)



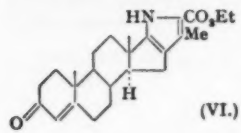
(IV; R′ = A.) (IV*a*; R′ = B.)

Evidence supporting this structure was furnished by surface-film measurements which, although not conclusive, appeared to favour a formulation of the angular type. There seems little doubt, however, that this conclusion must now be reversed and the compound assigned the linear structure (IV), the angular formulation being retained for the derivative from coprostan-3-one.

Biological study of (IV) was hampered by low solubility. We, therefore, examined the action of phenylhydrazine on methyl 3-keto*allo*- and 3 : 12-diketo-cholanate. Reaction occurred readily in acetic acid. The indolo-acids obtained by hydrolysis of the resulting methyl esters, however, proved insufficiently soluble to warrant further study. Attempts to convert the acid grouping of (IV*a*) into amino- *via* the hydrazide likewise proved disappointing. Reaction was ultimately achieved by heating the ester with 50% hydrazine hydrate at 140°, but the yield of hydrazide obtained was low.

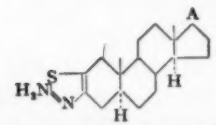


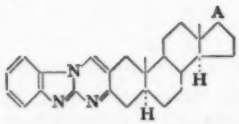
(V.)



(VI.)

(VII.)





(VIII.)

Compounds possessing a condensed pyrrole residue were synthesised by Knorr and Lange's reaction (*Ber.*, 1902, **35**, 2998), as extended by Treibs and Dinelli (*Annalen*, 1935, **517**, 152). Thus by condensing (I) with ethyl oximinoacetoacetate in the presence of zinc dust and acetic acid, ethyl 4′-methylpyrrolo(3′ : 2′-2 : 3)cholest-2-ene-5′-carboxylate (V) was obtained, although in only 10% yield. Cholest-4-en-3-one failed to react under these conditions. With androst-4-ene-3 : 17-dione it was hoped that reaction might be confined to the ketomethylene residue present in ring D, and a nucleus isomeric with that present in conessine obtained. The expected product, $C_{21}H_{33}O_2N$, to which the formulation ethyl 3-keto-4′-methylpyrrolo(3′ : 2′-16 : 17)androsta-4 : 16-diene-5′-carboxylate (VI) is assigned, was formed in such low yield, however, as to rob the method of practical significance. The reverse condensation of 16-oximinoandrost-4-ene-3 : 17-dione (Stodola and Kendall, *J. Org. Chem.*, 1942, **7**, 336) with ethyl acetoacetate in the presence of zinc dust and acetic acid led only to 16-ketotestosterone.

2′-Aminothiazolo(5′ : 4′-2 : 3)cholest-2-ene (VII) was prepared by reaction between 2-bromocholestan-3-one and thiourea in boiling *iso*propyl alcohol. 1′ : 9′ : 11′-Triazafluoreno(3′ : 2′-2 : 3)cholest-2-ene (VIII) was obtained in good yield by condensing 2-aminobenziminazole with 2-hydroxymethylenecholestan-3-one (Rosenheim and Stiller, *J.*, 1938, 357).

Only (II; R = NH_2) of the above compounds proved sufficiently soluble for biological study. Examination against a variety of organisms, kindly carried out for us by Dr. S. W. F. Underhill (Physiological Laboratories, The British Drug Houses, Ltd.), failed to reveal appreciable activity.

Experimental.

M. p.s are uncorrected. Microanalyses are by Drs. Weiler and Strauss, Oxford. Optical rotations were measured in chloroform solution in a 2-dm. tube.

Methyl 3-*Keto*allo*cholanate*.—Methyl 3-hydroxy*allo*chol-5-enate was prepared from the acid by Wallis and Fernholtz's method (*J. Amer. Chem. Soc.*, 1935, **57**, 1504). Catalytic hydrogenation of this

ester (15 g.) in acetone (130 ml.), in the presence of 5% palladised charcoal (10 g.), gave methyl 3-hydroxy-*allo*cholanate, m. p. 148—150°. Oxidation to the 3-keto-derivative was effected by Wieland and Dane's procedure (*Z. physiol. Chem.*, 1933, **215**, 15).

Quinolino(3′ : 2′-2 : 3)*cholest-2-ene* (II; R = H).—Cholestan-3-one (1·5 g.), *o*-aminobenzaldehyde (500 mg.) and potassium hydroxide (2·0 g.) in aqueous ethanol (80 ml.) were shaken with gentle warming, dissolution occurring, followed by separation of the condensation product. After 10—15 minutes the mixture was cooled, and the solids collected and purified from benzene–alcohol. *Quinolino*(3′ : 2′-2 : 3)*cholest-2-ene* formed crystals, m. p. 184°, $[\alpha]_D^{23}$ +63·7° (*c*, 1·489) (Found: C, 86·1; H, 10·3; N, 3·0. $C_{34}H_{49}N$ requires C, 86·6; H, 10·4; N, 3·0%).

Methyl quinolino(3′ : 2′-2 : 3)allo*chol-2-enate*, prepared from methyl 3-keto*allo*cholanate as above, formed crystals (from benzene–alcohol), m. p. 264° (Found: C, 80·6; H, 8·8; N, 3·4. $C_{28}H_{43}O_2N$ requires C, 81·1; H, 9·0; N, 3·0%).

4′-*Hydroxyquinolino*(3′ : 2′-2 : 3)*cholest-2-ene* (II; R = OH).—An intimate mixture of cholestanone (8 g.) and anthranilic acid (3·5 g.) was heated in a 100-ml. flask at 140° until a homogeneous liquid had been obtained; the temperature was then slowly raised to 200—220° and maintained there until the reaction mass had solidified. The resulting yellow solid was powdered, extracted thoroughly with benzene and alcohol, and finally crystallised from pyridine or nitrobenzene. 4′-*Hydroxyquinolino*-(3′ : 2′-2 : 3)*cholest-2-ene* (6 g.) formed very small white needles, m. p. >300° (Found: C, 83·4; H, 10·1. N, 3·1. $C_{34}H_{49}ON$ requires C, 83·8; H, 10·0; N, 2·9%).

4′-*Chloroquinolino*(3′ : 2′-2 : 3)*cholest-2-ene* (II; R = Cl).—The foregoing compound (15 g.) was heated with phosphorus pentachloride (7 g.) and phosphorus oxychloride (30 ml.) for 2 hours under reflux at 120—130°. The *product*, isolated in the usual way, crystallised from benzene–alcohol in leaflets, m. p. 204°, $[\alpha]_D^{23}$ +40·7° (*c*, 1·311) (Found: N, 3·3; Cl, 7·4. $C_{34}H_{48}NCl$ requires N, 2·8; Cl, 7·0%).

4′-*Phenoxyquinolino*(3′ : 2′-2 : 3)*cholest-2-ene* (II; R = OPh).—The fore-going chloro-derivative (1·5 g.) and phenol (2·0 g.) were heated at 150—160° for 2 hours, after which the cooled mass was digested with sodium hydroxide solution and the product extracted with chloroform. Purification by adsorption on alumina, followed by elution with ethanol, gave 4′-*phenoxyquinolino*(3′ : 2′-2 : 3)*cholest-2-ene*, needles (from aqueous ethanol), m. p. 157° (softens at 112—113° with loss of 0·75H_2O), $[\alpha]_D^{23}$ +36·3° (*c*, 0·716) (Found, on anhydrous material: C, 84·8; H, 9·1; N, 2·7. $C_{40}H_{53}ON$ requires C, 85·1; H, 9·5; N, 2·5%).

4′-*Aminoquinolino*(3′ : 2′-2 : 3)*cholestane* (II; R = NH_2).—The foregoing chloro-derivative (2·0 g.) dissolved in *p*-cresol (20 g.) was treated at 200° with a stream of dry ammonia for 70 minutes. The cooled mass was agitated with excess of sodium hydroxide solution, and the solids were extracted with hot benzene. Addition of light petroleum (b. p. 100—120°) to the hot concentrated extract gave the 4′-*amine* on cooling, as platelets, m. p. 217°, $[\alpha]_D^{23}$ +25·6° (*c*, 0·421) (Found: C, 84·1; H, 9·7; N, 5·8. $C_{34}H_{50}N_2$ requires C, 84·0; H, 10·2; N, 5·8%).

Methyl 4′-*hydroxyquinolino*(3′ : 2′-2 : 3)allo*cholenate*, prepared from methyl 3-keto*allo*cholanate (10·6 g.) and anthranilic acid (4·4 g.), formed a white powder, m. p. >300° (Found: C, 78·7; H, 8·2; N, 2·5. $C_{32}H_{43}O_3N$ requires C, 78·5; H, 8·7; N, 2·8%).

4′-*Chloroquinolino*(3′ : 2′-2 : 3)allo*chol-2-enic acid* (IIa; R = Cl), obtained by treating the foregoing compound with phosphorus pentachloride–oxychloride, formed plates [from benzene–light petroleum (b. p. 80—100°)], m. p. 193°, $[\alpha]_D^{23}$ +34·7° (*c*, 0·748) (Found: C, 75·1; H, 8·1; N, 3·4; Cl, 7·7. $C_{31}H_{46}O_2NCl$ requires C, 75·3; H, 8·1; N, 2·8; Cl, 7·2%).

4′-*Aminoquinolino*(3′ : 2′-2 : 3)allo*chol-2-enic acid* (IIa; R = NH_2) separated from benzene–light petroleum (b. p. 100—120°) in pale yellow crystals, m. p. 198° (Found: C, 78·5; H, 9·2; N, 5·9. $C_{31}H_{48}O_2N_2$ requires C, 78·4; H, 8·8; N, 5·9%).

4′-*Hydroxyquinolino*(3′ : 2′-2 : 3)*cholesta-2 : 4-diene* (III) separated from nitrobenzene in a yellow felted mass of very small needles, m. p. >300° (Found: C, 85·0; H, 9·3; N, 2·9. $C_{34}H_{47}ON$ requires C, 84·1; H, 9·6; N, 2·9%).

Methyl Indolo(3′ : 2′-2 : 3)allo*chol-2-enate*.—Methyl 3-keto*allo*cholanate (2·5 g.) and redistilled phenylhydrazine (5 g.) were heated with acetic acid (80 ml.) on the water-bath for 1 hour. The mixture was then poured into water. The precipitated pale yellow solids were collected and crystallised from benzene–ethanol, giving *methyl indolo*(3′ : 2′-2 : 3)allo*chol-2-enate* in white crystals, m. p. 194°, $[\alpha]_D^{23}$ +55·6° (*c*, 1·025) (Found: C, 80·6; H, 9·1; N, 3·1. $C_{31}H_{43}O_2N$ requires C, 80·6; H, 9·5; N, 3·0%).

Indolo(3′ : 2′-2 : 3)allo*chol-2-enic acid hemihydrate* (IVa), prepared by hydrolysis of the foregoing ester, formed from aqueous ethanol crystals which melted at 180°, resolidified, and finally melted at 220° (Found: C, 78·3; H, 9·6; N, 3·6. $C_{30}H_{41}O_2N,\frac{1}{2}H_2O$ requires C, 78·6; H, 9·2; N, 3·0%).

Methyl 12-*ketoindolo*(3′ : 2′-2 : 3)*chol-2-enate*, prepared from methyl 3 : 12-diketocholanate, formed crystals (from benzene–ethanol), m. p. 197°, $[\alpha]_D^{23}$ +224·8° (*c*, 0·889) (Found: C, 77·7; H, 8·7; N, 2·6. $C_{31}H_{41}O_3N$ requires C, 78·3; H, 8·6; N, 2·9%).

The corresponding *acid monohydrate*, obtained by hydrolysis of the foregoing ester and crystallised from aqueous ethanol, had m. p. 232° (decomp.) (Found: C, 75·1; H, 8·1. $C_{30}H_{39}O_3N,H_2O$ requires C, 75·1; H, 8·5%).

Indolo(3′ : 2′-2 : 3)allo*chol-2-enoylhydrazide*, prepared by heating the corresponding methyl ester (2·5 g.) and hydrazine hydrate (10 ml. of 50%) in a sealed tube at 140° for 5 hours, separated from aqueous alcohol in crystals, m. p. 240—242° (Found: C, 77·3; H, 9·3; N, 8·8. $C_{30}H_{43}ON_3$ requires C, 78·0; H, 9·3; N, 9·1%).

Ethyl 4′-*Methylpyrrolo*(3′ : 2′-2 : 3)*cholest-2-ene-5′-carboxylate* (V).—Cholestanone (8 g.) and ethyl oximinoacetoacetate (3·2 g.) in acetic acid (170 ml.) were heated gently under reflux, and zinc dust (6 g.) was gradually added with efficient mechanical stirring during 20 minutes. Refluxing was continued for a further 3 hours, whereafter unreacted zinc was removed and washed with acetic acid and

ethanol, and the bulked filtrate and washings were poured into water (1 l.) with stirring. The precipitated solids (10 g.) were collected, dried, extracted with alcohol (which removed unchanged cholestanone), and crystallised from benzene–light petroleum (b. p. 60—80°), to give the desired *product*, (700 mg.), m. p. 212°, $[\alpha]_D^{26}$ +34·1° (*c*, 0·468) (Found: C, 79·9; H, 10·2; N, 3·2. $C_{29}H_{43}O_2N$ requires C, 80·0; H, 10·7; N, 2·8%).

Ethyl 3-Keto-4'-methylpyrrolo(3' : 2'-16 : 17)androsta-4 : 16-diene-5'-carboxylate (VI).—When androst-4-ene-3 : 17-dione (5 g.) and ethyl oximinoacetoacetate (3·2 g.) in acetic acid (170 ml.) were treated with zinc dust (10 g.) under reflux, a very low yield of this *pyrroloandrostadiene* was obtained, as crystals [from benzene–light petroleum (b. p. 60—80°)], m. p. 204—220° (partial decomp.) (Found: C, 75·7; H, 8·2; N, 3·5. $C_{25}H_{33}O_2N$ requires C, 75·9; H, 8·3; N, 3·5%).

16-Oximinoandrost-4-ene-3 : 17-dione.—The following method was employed (cf. Stodola and Kendall, *loc. cit.*): Androst-4-ene-3 : 17-dione (10 g.) and amyl nitrite (4·6 g.) were added to sodium (1·0 g.) in absolute ethanol (80 ml.) and the mixture heated at 60—70° for 30 minutes. After 2 days at room temperature the dark red solution was poured into ice-water (750 ml.) and extracted with ether, and the aqueous layer acidified with acetic acid. Crystallisation of the precipitated solids from benzene–light petroleum (b. p. 60—80°) gave 16-oximinoandrost-4-ene-3 : 17-dione as a yellow-brown solid, darkening above 220° and melting at 244° (decomp.), $[\alpha]_D^{26}$ +240·8° (*c*, 0·745) (Found: C, 72·1; H, 7·5; N, 4·2. Calc. for $C_{19}H_{25}O_3N$: C, 72·3; H, 7·9; N, 4·4%). Stodola and Kendall (*loc. cit.*) give 230° and 237—238°, respectively.

16-Ketotestosterone.—Reduction of 16-oximinoandrost-4-ene-3 : 17-dione (2·4 g.) and ethyl acetoacetate (8 g.) in 95% acetic acid (100 ml.) with zinc dust (7 g.) under reflux gave *16-ketotestosterone*, needles (from benzene–light petroleum), m. p. 189° (Found: C, 75·1; H, 8·6. $C_{19}H_{26}O_3$ requires C, 75·5; H, 8·6%).

2'-Aminothiazolo(5' : 4'-2 : 3)cholest-2-ene (VII).—2-Bromocholestanone (1·5 g.) and thiourea (250 mg.) were heated under reflux in *iso*propyl alcohol (30 ml.) for 40 minutes. After cooling, the mixture was treated with hot sodium carbonate solution, and the solids were collected and crystallised from benzene. *2'-Aminothiazolo(5' : 4'-2 : 3)cholest-2-ene* formed crystals, m. p. 266°, $[\alpha]_D^{26}$ +64·4° (*c*, 0·496) (Found: C, 76·0; H, 10·1; N, 5·8; S, 6·9. $C_{28}H_{46}N_2S$ requires C, 76·0; H, 10·4; N, 6·3; S, 7·2%).

1' : 9' : 11'-Triazafluoreno(3' : 2'-2 : 3)cholestane (VIII), prepared by heating 2-hydroxymethylenecholestan-3-one (1·7 g.) with 2-aminobenziminazole (500 mg.) at 190° and finally at 220°, crystallised from chloroform–alcohol in yellow plates, m. p. 295°, $[\alpha]_D^{24}$ +78·1° (*c*, 0·467) (Found: C, 81·1; H, 9·6; N, 8·7. $C_{35}H_{49}N_3$ requires C, 82·2; H, 9·6; N, 8·2%).

The authors thank Prof. J. R. Partington, D.Sc., M.B.E., for providing research facilities for one of them (H. A.), who is also indebted to the Egyptian Government for a Scholarship.

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203. *The Constitution of Copper Peroxide and the Catalytic Decomposition of Hydrogen Peroxide.*

By ABRAHAM GLASNER[1]

On the evidence of photometric and gasometric measurements it is concluded that copper peroxide is formed by the simple addition of a HO_2 radical to cupric hydroxide and therefore should have the formula CuO,O_2H,aq. The measurements were made in the presence of sodium citrate which kept the intensely brown peroxide in solution. The formation of the copper peroxide is promoted by sodium hydroxide, but is retarded by an excess of citrate.

Copper peroxide is unstable; therefore its concentration in solutions in which it is prepared is a function of time, yielding bell-shaped curves (see Fig. 1). In solutions of otherwise similar composition, the maxima of the curves are proportional to the 1·5 power of the initial concentration of the hydrogen peroxide. These maxima may be regarded as corresponding to a steady state and can be represented by an equilibrium constant K, which was recorded for a few series of solutions at two temperatures, 10° and 20°.

The catalytic decomposition of hydrogen peroxide is shown to be proportional to the concentration of copper peroxide present at any moment in the solution. The rate of evolution of oxygen was found to correspond approximately to the order $\frac{1}{2}$ with respect to the hydrogen peroxide, but this is explained by showing that it is a function of the equilibrium constants K.

IT was suggested, in discussing the blue perchromates (Glasner, *J.*, 1950, 2795), that the HO_2 molecule is involved in their formation, and the suggestion afforded a feasible explanation

of the properties of the perchromates and their function in the catalytic decomposition of hydrogen peroxide. It seemed probable, therefore, that some of the anomalies observed with the peroxides of the transitional elements might be explained on similar lines, and accordingly the brown copper peroxide has now been studied.

It is known that cupric salts in alkaline solution give with hydrogen peroxide a brown, very unstable precipitate which most investigators have tacitly assumed to have the composition $CuO_2H_2O_2$, but analysis always gave a ratio $CuO : H_2O_2 > 1$, and this was ascribed to the unstable nature of this compound (Aldridge and Applebey, *J.*, 1922, **121**, 238; Teletov and Veleshinetz, *Ukrain. Chem. J.*, 1931, **6**, Sci., 53; *Chem. Abs.*, 1931, **25**, 3635; Mueller, *Bull. Soc. chim.*, 1936, **3**, 1913). Another red oxide, given the formula Cu_2O_3, was prepared by Buntin and Vlasov (*Acta Univ. Voronegiensis*, 1935, **8**, No. 4, 6; *Chem. Abs.*, 1938, **32**, 6598$_8$; Zhuze and Starchenko, *J. Exp. Theor. Phys. U.S.S.R.*, 1940, **10**, 331; *Chem. Abs.*, 1940, **34**, 7687). Wieland and Stein (*Z. anorg. Chem.*, 1938, **236**, 361), from a preparation at −79°, isolated and analysed a copper peroxide and gave it the formula $HO_2{\cdot}Cu{\cdot}O_2{\cdot}Cu{\cdot}O_2H$. (They gave a similar formula to a ferric peroxide which they prepared.) As they did not determine the molecular wieght of their copper peroxide, it might as well be written as the monomer $CuO{\cdot}O_2H$, formed by the addition of HO_2 to CuO, and the experimental results at 10° to 30° now described are believed to confirm this suggestion.

Experimental.

In presence of sodium citrate, the brown peroxide was not precipitated but formed an intensely coloured homogeneous solution which slowly decomposed evolving oxygen, thereby regaining its original pale blue colour. Such solutions of diverse composition were therefore studied. The measurements were made with a gasometer and a Hellige "panphotometer" to which a small thermostat enveloping the glass vessel had been attached, the same technique being used as described for the perchromates (Bobtelsky, Glasner, and Bobtelsky-Chaikin, *J. Amer. Chem. Soc.*, 1945, **67**, 966). The stock solutions were: (1) $CuSO_4.5H_2O$, Schering–Kahlbaum, "zur Analyse," 0·1038M. or 0·107M., determined by electrolysis. (2) Sodium citrate B.P., 0·108M., determined by conductometric titration with a cobalt salt of known concentration. (3) Sodium hydroxide, "for analysis," 0·1631M., free from carbonate. (4) Hydrogen peroxide, Merck's "perhydrol" diluted, and the concentration determined for each series of experiments by titration with standard permanganate solution.

The solutions for each experiment were made up to a total volume of 50 ml., and the reaction vessels were kept in thermostats at the temperatures indicated.

In the photometric measurements a 470 mμ. filter was found to be best, for with this the blue copper solution has a minimum, and the brown peroxide solution a maximum estinction. As controls, readings were taken also with a 500-mμ. filter (the ratio of the extinctions E_{470}/E_{500} was *ca.* 1·71). The depth of the solution in the photometer was always 5 mm., and for each measurement a new portion of the solution was taken.

Results.—Fig. 1, curve *a*, shows the change with time at 20° of the extinction of a solution having the composition (in millimols./l.): $CuSO_4$, 2·14; Na_3Cit, 4·32; NaOH, 8·328; H_2O_2, 30·2. There is an initial lag, then the extinction rises quickly to a maximum followed by a slower decrease. Curve *b* shows the evolution of oxygen from a similar solution. Here we have again a lag, and the curve is on the whole S-shaped. There is a complete agreement between all the phases of the two curves including a coincidence between the maximum extinction and the steepest part of the S-curve. Hence, there can be no doubt that the decomposition of the hydrogen peroxide and the formation of the copper peroxide are not two independent reactions, but represent two aspects of a series of consecutive reactions, the brown copper peroxide being an intermediate in the catalytic decomposition of the hydrogen peroxide.

When the concentration of any of the components in the solutions was changed, the results were rather complicated, since the relative amounts of copper, citrate, and hydroxide seemed to be all interrelated.

Variation of sodium hydroxide concentration. In Fig. 2 are given a series of curves showing the catalytic decomposition of hydrogen peroxide in solutions containing different amounts of sodium hydroxide but otherwise identical. The final concentrations of the reagents (in millimols./l.) were: $CuSO_4$, 2·076; Na_3Cit, 4·32; H_2O_2, 25·2; NaOH, 5·82—9·98. It is seen that an increase in the concentration of sodium hydroxide shortens the time lag and increases the velocity of decomposition up to about 5 mols. of sodium hydroxide to each mol. of copper sulphate. A further excess of sodium hydroxide reduces somewhat the velocity of decomposition and may result also in the formation of a brown precipitate.

At the lower limit, catalytic decomposition can take place only if the molar concentration of sodium hydroxide is greater than that of the citrate. With solutions containing a 1 : 1 molar ratio of copper to citrate, only slightly more than 1 mol. of sodium hydroxide is necessary for the decomposition of hydrogen peroxide to occur.

The copper citrate catalyst. Some light on the state of the copper in the solution before the formation of the peroxide is obtained from a consideration of the curves *c* and *d* (photometric) and *e* and *f* (gasometric) in Fig. 1. These pairs of curves were obtained from solutions having exactly the same composition, and only the order of the addition of the various reagents was altered: in all experiments hitherto discussed and also in *c* and *e* hydrogen peroxide was added last to the reaction mixture, but in

d and *f* copper sulphate was the reagent added last. It is seen that in the photometric curve *d* the time lag is entirely absent, and in the gasometric curve *f* it is greatly shortened.

Again, on mixing the copper and citrate solutions and adding this mixture to a dilute alkaline hydrogen peroxide solution, the curves obtained are like *c* and *e* to which hydrogen peroxide was added last, showing a lag. Hence, it may be concluded that for the formation of the copper peroxide the

FIG. 1.

Formation and decomposition of copper peroxide. A comparison of photometric and gasometric measurements.

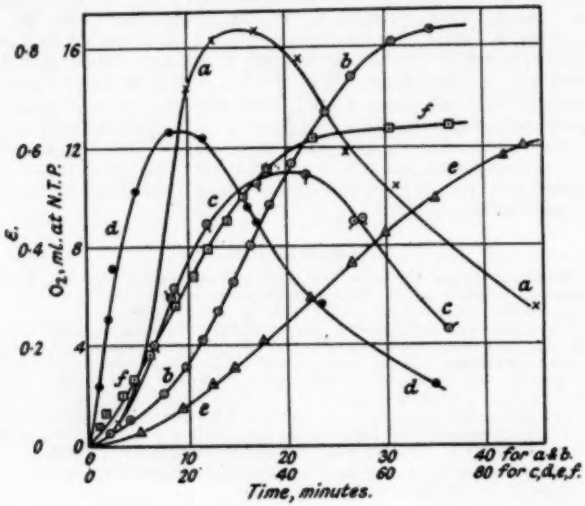
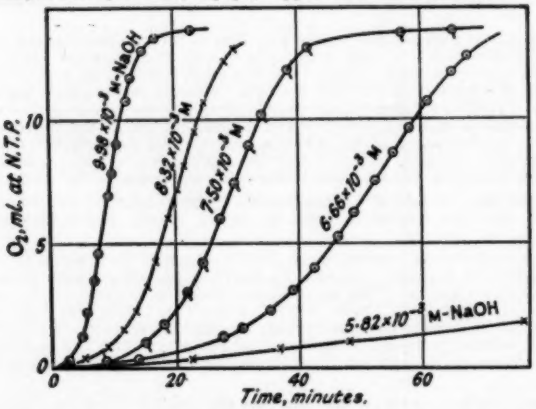


FIG. 2.

Catalytic decomposition of H_2O_2 *by copper citrate:* NaOH *varied.*



pre-existence of a basic copper compound is necessary, and the rôle of the citrate is merely to keep the copper in solution, thus affording a homogeneous reaction. The effect of varying the concentration of the copper sulphate could not be studied independently of the concentration of the citrate and sodium hydroxide, as stated above, so the order of reaction with regard to copper sulphate could not be determined directly.

Variation of hydrogen peroxide concentration. (a) Photometric measurements. Fig. 3 shows the variation with time at 20° of the extinction of a series of solutions having the general composition (in

millimols./l.) = $CuSO_4$, 1·038; Na_3Cit, 2·16; NaOH, 8·328; with various concentrations of hydrogen peroxide in a total volume of 50 ml. On increasing the concentration of hydrogen peroxide a maximum extinction $E_{470} = 0·540$ is obtained, *i.e.*, at this or higher concentrations of hydrogen peroxide, all the copper in the solution is converted into the peroxide and so the molecular extinction of the brown

FIG. 3.

Extinction–time curves of copper peroxide : H_2O_2 varied.

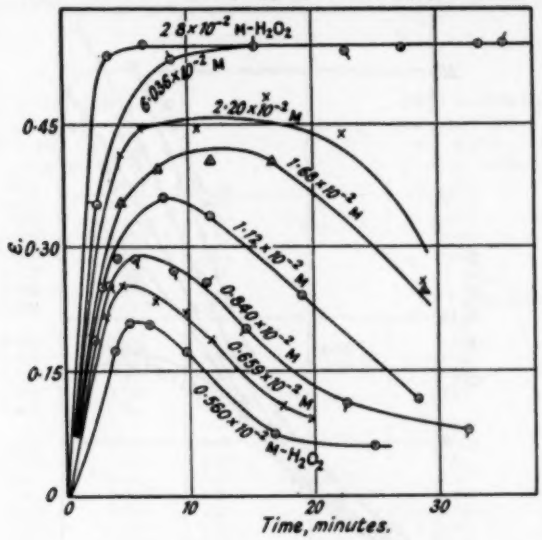


TABLE I.

Equilibrium constants, from photometric measurements.

(*a*) At 20°.

$1·038 \times 10^{-3}$M-$CuSO_4$; $8·328 \times 10^{-3}$M-NaOH; $E_{100\%} = 0·540$.

$H_2O_2 \times 10^3$.	E_{470}.	$K \times 10^3$.
0·560	0·213	0·643
0·659	0·255	0·598
0·840	0·294	0·644
1·120	0·360	0·593
1·680	0·420	0·622
2·196	0·456	0·599
		Mean 0·618

$2·14 \times 10^{-3}$M-$CuSO_4$; $8·328 \times 10^{-3}$M-NaOH; $E_{100\%} = 1·113$.

3·04	0·840	1·72

(*b*) At 10°.

$2·076 \times 10^{-3}$M-$CuSO_4$; $8·328 \times 10^{-3}$M-NaOH; $E_{100\%} = 1·080$.

$H_2O_2 \times 10^3$.	E_{470}.	$K \times 10^3$.
0·750	0·305	1·65
0·844	0·365	1·52
1·000	0·435	1·47
1·250	0·510	1·65
2·110	0·740	1·42
		Mean 1·54

$1·038 \times 10^{-3}$M-$CuSO_4$; $8·328 \times 10^{-3}$M-NaOH; $E_{100\%} = 0·540$.

0·540	0·225	0·539
0·810	0·314	0·504
1·080	0·372	0·481
1·350	0·415	0·472
		Mean 0·499

copper peroxide can be calculated. Each individual curve in Fig. 3 attains a maximum extinction ($E_{max.}$) at a definite moment. At these maximum points the velocities of formation and decomposition of the peroxide are equal; *i.e.*, $E_{max.}$ is a point of " pseudo equilibrium " or steady state and we may write

$$[Cu^{++}]^m[H_2O_2]^n/[Per]^p = (b - E_{max.})^m a^n/E^p_{max.} = K$$

where a is the initial concentration of hydrogen peroxide and b that of the copper salt expressed in the same units as $E_{max.}$. The experimental values of $E_{max.}$ being used, the indices in this equation were found by trial; on taking $m = p = 1$ and $n = 1·5$ fairly constant values for K were obtained as shown in Table I(*a*).

In Table I(*b*) are summarized the results of two other series of experiments at 10°. The ratio of citrate to copper sulphate in all the solutions was slightly more than 2 : 1, and it should be remembered that only solutions containing similar amounts of the three reagents, copper, citrate, and hydroxide, should be compared. With these considerations, and account being taken of the single solution with a

FIG. 4.

Catalytic decomposition of H_2O_2 *:* H_2O_2 *varied.*

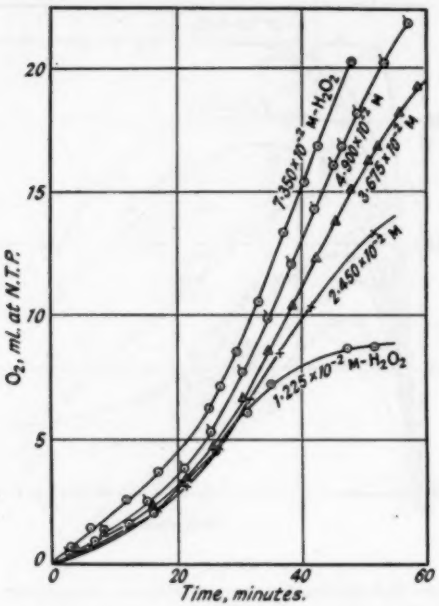
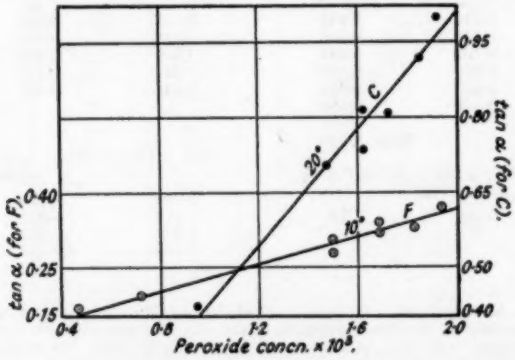


FIG. 5.

Relation between decomposition rate and copper peroxide concentration.



concentration of 2·14 × 10^{-3}M-$CuSO_4$ at 20°, the temperature coefficients of K are 1·24 and 1·12. The maximum extinctions obtained are slightly higher at 10°, but the time taken for the attainment of these maxima was far shorter at 20°.

(*b*) Gasometric measurements. Curves in Fig. 4 represent the evolution of oxygen at 20° from a series of solutions having the general composition (millimols./l.): $CuSO_4$, 2·14; Na_3Cit, 4·32; NaOH,

7·495. The concentration of hydrogen peroxide was varied; total volume 50 ml. Hydrogen peroxide was the reactant added last. The general form of the curves has been discussed (p. 905). The increase in the concentration of hydrogen peroxide has a regular accelerating effect on the velocity of decomposition (unless the hydrogen peroxide is added in a very large excess), which is best demonstrated by the tangents of the inflection points on the S-curves: the middle parts of the curves are very nearly straight for a considerable period, and therefore the tangents of the angles these lines make with the abscissa (tan α) are most convenient for a quantitative comparison.

Table II (*a*) shows that tan α divided by the square root of the hydrogen peroxide concentration (C) is

TABLE II.

Rate of evolution of oxygen.

NaOH, M × 10³.	H_2O_2, M × 10³ = C × 10³.	tan α.	tan α/$C^{0·5}$.
	$2·14 \times 10^{-3}$M-$CuSO_4$. (*a*) At 20°.		
6·246 (Series A)	1·525	0·197	1·59
	1·525	0·189	1·53
	2·768	0·250	1·50
	3·050	0·306	1·75
	3·050	0·280	1·60
	4·152	0·327	1·60
	5·536	0·408	1·74
	6·920	0·437	1·66
7·495 (Series B)	1·225	0·280	2·54
	2·450	0·375	2·40
	3·675	0·495	2·58
	4·900	0·580	2·62
	7·350	0·640	2·36
8·328 (Series C)	1·231	0·435	3·92
	2·462	0·703	4·48
	3·04	0·815	4·68
	3·04	0·735	4·21
	3·693	0·810	4·22
	4·924	0·920	4·16
	6·08	0·950	3·85

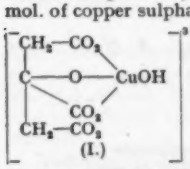
NaOH, M × 10³.	H_2O_2, M × 10³ = C × 10³.	tan α.	tan α/$C^{0·5}$.
	$2·076 \times 10^{-3}$M-$CuSO_4$. (*b*) At 30°.		
7·50 (Series D)	1·362	0·560	4·78
	2·724	1·210	7·33
	4·086	1·320	6·47
	5·448	1·480	6·36
	6·810	1·730	6·63
	(*c*) At 10°.		
7·50 (Series E)	4·42	0·272	1·32
	6·63	0·286	1·11
	8·84	0·338	1·14
	8·84	0·338	1·14
	13·26	0·316	0·87
8·328 (Series F)	0·584	0·165	2·16
	0·876	0·190	2·03
	2·52	0·280	1·76
	2·52	0·306	1·93
	3·78	0·320	1·65
	3·78	0·340	1·75
	5·04	0·330	1·47
	7·56	0·370	1·35

a constant (k), not only for the solutions represented in Fig. 4, but also for two other series of solutions having a different concentration of alkali; *i.e.*, the velocity of hydrogen peroxide decomposition is proportional to the square root of this reagent in most of the solutions studied.

Some experiments were repeated at 30° and at 10°. The results are summarized in Table II, (*b*) and (*c*). The temperature coefficient calculated from the average of the rate constants k (wherever this seems to hold) is about 2·5.

DISCUSSION.

We have seen that the decomposition of hydrogen peroxide is catalysed by the copper citrate complex only in solutions containing more than 1 mol. of sodium hydroxide for each mol. of copper sulphate. Bobtelsky and Jordan (*J. Amer. Chem. Soc.*, 1945, **67**, 1831) assigned



(I.)

to the complex produced under similar conditions the formula (I), containing one hydroxyl group directly attached to the copper atom. Hence it may be assumed that the peroxide studied in this paper is similarly constituted, and undergoes the same reactions as the copper peroxide produced in the absence of the citrate. In the following we shall abbreviate (I) to $(Cit\,CuOH)^{3-}$. From the equilibrium constants K (Table I) we may conclude that the brown peroxide (II) ([Per] for short) is formed from one molecule of the basic copper complex and 1·5 molecules of hydrogen peroxide, and also that the decomposition of the per-compound is of the first order. This suggests the following series of reactions:

$$(1)\quad [Cit\,CuOH]^{3-} + HO_2^- \longrightarrow \underset{(II.)}{[Cit\,CuO_2]^{3-}} + H_2O$$

$$(2)\quad (II) \longrightarrow \underset{(III.)}{[Cit\,Cu]^{3-}} + O_2$$

$$(3)\quad (III) + H_2O_2 \longrightarrow \underset{(I.)}{[Cit\,CuOH]^{3-}} + OH\ (rapid)$$

For reaction (1) it is assumed (Glasner, *J.*, 1950, 2798) that in all hydrogen peroxide solutions the following equilibria exist :

$$H_2O_2 \rightleftharpoons 2OH \text{ and } HO + H_2O_2 \rightleftharpoons HO_2 + H_2O$$

and therefore

$$[HO_2] = K_{HO_2}[H_2O_2]^{1\cdot5}$$

Thus the odd-electron ion O_2^- in the peroxy-compound (II) may be made responsible for the intense colour of this per-compound and its labile nature.

In analogy with the perchromates, it is further considered that the odd electron from the O_2^- is transferred to the copper, which is thus reduced to the univalent state. This could be tested by examining the magnetic susceptibility of (II).

According to reaction (2), the evolution of oxygen in the gasometric measurements should be proportional to the concentration of the per-compound present at any moment in the solution. Fig. 1 shows this to be the case. Furthermore, the K values from Table I may be used to calculate the concentration of the per-compound at the steady state, for the series of solutions C (at 20°) and F (at 10°) by the equation

$$[\text{Per}] = b[H_2O_2]^{1\cdot5}/(K + [H_2O_2]^{1\cdot5})$$

where all the symbols have the meanings previously assigned to them. When [Per] is plotted against tan α, straight lines are obtained as shown in Fig. 5. This not only proves the unimolecular decomposition of (II), but also confirms the correctness of the equilibrium equation at the steady state.

It should be added that the proportionality found between tan α and the square root of the initial concentration of the hydrogen peroxide should hold only for a limited range. This will be seen on considering the two extreme cases :

$$\text{(A)} \quad K \gg [H_2O_2]^{1\cdot5} \quad [\text{Per}] = b[H_2O_2]^{1\cdot5}/K$$

and

$$\text{(B)} \quad K \ll [H_2O_2]^{1\cdot5} \quad [\text{Per}] = b$$

showing that the order of the reaction with respect to the initial concentration of the hydrogen peroxide ought to vary from 1·5 to zero. As has been noted (p. 909), a large excess of hydrogen peroxide does not increase tan α after this has attained a maximum value (zero order).

In order to close the catalytic cycle it is plausible to assume the rapid reaction (3) in which the copper is reoxidized to the bivalent state. It was observed during the experiments that the brown colour in the solutions persisted for some time after all the hydrogen peroxide was decomposed (see Fig. 3). This brown colour may be due to the univalent copper which is slowly oxidized in the air. The hydroxyl radical produced by reaction (3) possibly oxidizes another univalent copper complex ion, or two of them reunite to reform hydrogen peroxide. In any case, it would be worth while to try the use of the copper citrate complex in the polymerization of slightly alkaline solutions in place of Fenton's reagent.

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204. *Selective Diffusion into Ion-exchange Resins. A New Method for the Purification of the Direct Cotton Dyes.*

By R. W. Richardson.

Purification of direct cotton dyes by an ion-exchange technique is described. Use is made of the observation that selective diffusion of ionic species into the bulk of the resin structure depends on the molecular dimensions of the ion. It has been shown that by this means the large organic anions of the dye may be effectively separated from those of the much smaller diluent salts.

Isolation of pure direct cotton dyes from the crude salted-out products is an essential preliminary to all experiments on the fundamental physical chemistry of dyeing. For this purification Robinson and Mills (*Proc. Roy. Soc.*, 1931, *A*, **131**, 596) recommended a procedure which has since been adopted by *inter al.*, Boulton, Delph, Fothergill, and Morton (papers, from 1935 onwards, in *J. Text. Inst.*, *J. Soc. Dyers Col.*) in their quantitative investigations. This method

consists in repeated precipitation of the dye from aqueous solution by pure sodium acetate until free from inorganic anions, followed by extraction of the dried dye with ethanol to remove the acetate. The method is tedious, often involving filtrations of near-colloidal precipitates; further it has now been shown that prolonged extractions are needed to remove last traces of sodium acetate; varying amounts of the dye itself are often removed during this treatment depending on the nature of dye, its moisture content, and the purity of the ethanol.

The purifications described below are based upon the fact that the ion-exchangers used are capable of acting as " molecular sieves." The resins contain a network of pores of various sizes, as is shown by an increased capacity as the size of the adsorbed molecule is reduced. It has been shown (Richardson, *Nature*, **1949**, **164**, 916; Faraday Soc. Discussion, Chromatographic Analysis, 1949, p. 159) that ions of an average diameter of about 30 A., corresponding approximately to those of the direct colours based on benzidine derivatives are, in effect, completely prevented from entering the resin. Reaction takes place at the surface but this corresponds to $<0{\cdot}1\%$ of the available exchange centres. While molecular-sieve effects

FIG. 1.

Absorption of Sky Blue FF on Deacidite B; 2 g./25 ml.; 25°.

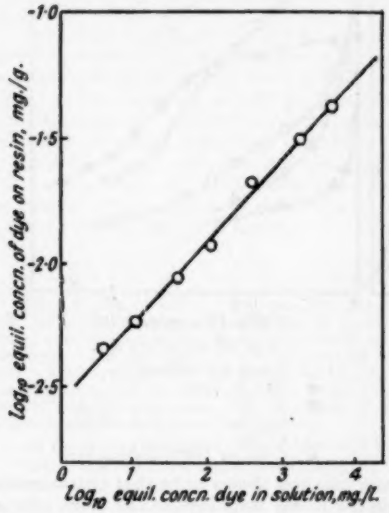
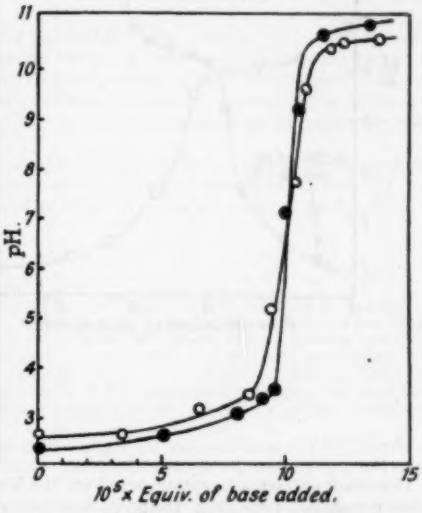


FIG. 2.

Titration curve for Sky Blue FF acid (10^{-4} equiv. in 20 ml.).



determine in varying degrees the behaviour of all molecules in contact with porous solids, only in the case of gases have separations by a total (*i.e.*, a completely selective) sieve action been recorded (Barrer, *Quart. Reviews*, **1949**, **3**, 293). Ion-exchange resins of well-defined micropore size should thus have extended usefulness by virtue of a new, and variable, physical property.

Exchange from aqueous solutions of the crude dyes on a sulphonic acid resin gave acidic, ash-free effluents containing the derived dye acid and the inorganic acids from the salts. The solutions, with either a weakly or a strongly basic exchanger, yielded effluents from which the inorganic acid alone had been removed.

The use of a strongly-basic resin to remove carbon dioxide was later found necessary. Even in the absence of carbonate impurity, dissolved carbon dioxide on neutralisation may yield sufficient alkali carbonate to represent several % of impurity calculated on the weight of pure dye.

Many dye coupling components containing ionisable groups are sufficiently small to be essentially completely adsorbed in the quantities in which they would normally be expected to be found. For example, 2-aminonaphthalene-1-sulphonic acid is able to reach 94% of the

ionic centres available to sulphuric acid in the weakly basic resin Deacidite B (Richardson, *loc. cit.*). With dyes smaller than those based on benzidine, *e.g.*, those of the " acid " class prepared from the naphthylamines, as much as 1·5% of the resin capacity may be saturated. Regeneration of the resin then becomes troublesome as the slow outward diffusion of the dye makes its complete removal difficult. With the materials available, however, it was possible to purify sodium 8-acetamido-1-hydroxy-2-phenylazonaphthalene-5-sulphonate by increasing the rate of flow of solution through the column.

FIG. 3.

Titration curve for the carboxylic dye Chlorazol Fast Red F (250 mg./100 ml.).

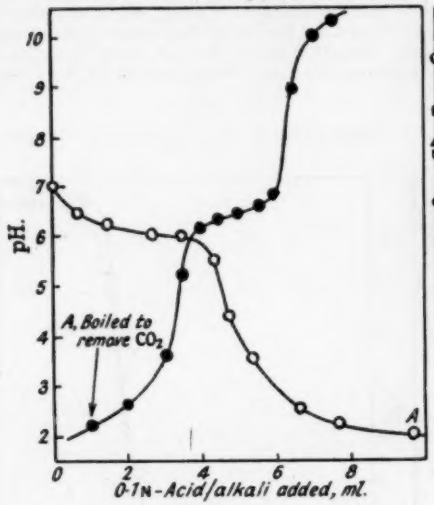


FIG. 4.

Electrometric titration of Sky Blue FF preparations.

For 100 mg. of dry dye.

○ *Crude dye (250 mg.).*
● *Cf. (5), Table.*
■ *Cf. (3)* ,,
□ *Cf. (4a)* ,, *(ash, 29·5%).*
△ *Cf. (2)* ,,
▲ *Calc. for 100% dissociation*

The small surface adsorption noted for the larger ions was shown to be that characteristic of the Freundlich type (Fig. 1) and is therefore similar to the behaviour of the much smaller inorganic acids in aqueous solution (Myers, Eastes, and Urquart, *Ind. Eng. Chem.*, 1941, **33**, 1270).

The sodium salts of the dye acids were prepared by neutralisation with alkali hydroxide to pre-determined pH values. These were found to be pH 7 for sulphonic acids and pH 8 for those dyes also containing carboxyl groups (Figs. 2 and 3). The removal of alkali, added in excess, by weakly acidic resins containing phenolic hydroxyl or partly saturated carboxyl groups was unsuccessful. Both types of exchanger exhibited a small " salt-splitting " capacity, giving solutions of sufficient acidity (pH 3—4) to affect the dye-absorption characteristics of some classes of dyes. The effluents obtained were, however, more easily adjusted to the correct pH values than the original strongly acid solutions.

With dyes yielding water-insoluble sulphonic acids exchange from aqueous-organic solvents was unsatisfactory, owing to the necessity for the removal of the organic solvent when recovery of the solid dye was otherwise not required. For these and for " acid-labile " dyes the alternative " reverse deionisation " using strongly basic exchangers was therefore examined, since the solutions under these conditions remain alkaline. It was concluded that if the molecular-sieve effect was shown with this type of resin (their use in the acid-absorption experiments in place of the weaker resins, described above, had not then been investigated) an effluent containing the dye (sodium salt) and alkali hydroxide should result.

This was found to be the case : only slight, apparently irreversible or very slowly reversible, adsorption takes place with large dye molecules. Less than 0·5% of inorganic salts, based on the weight of dye, was detected in the effluent. The removal of excess of alkali was then carried out as previously described. During this work it was found necessary to prevent carbonation of the alkaline effluent since buffering caused by alkali hydrogen carbonate made final pH adjustment impossible. Alkali carbonate if present in the crude dye is removed by the strongly basic resin (Davies and Nancollas, *Nature*, **1950**, **165**, 237).

The ash contents recorded for the typical dyes examined (Sky Blue FF, Colour Index No. 518) were less than those obtained in routine preparations by the sodium acetate method. It was then shown (Fig. 4) that in the latter preparations small amounts of sodium acetate were retained even after 7 hours' rapid Soxhlet extraction. The lowest ash content obtained by this method was 0·5—1·0% higher than that obtained by ion exchange. The sample then still contained traces of sodium acetate which was shown to be difficult to remove unless the dye was kept finely divided during extraction. The analytical values suggest that the overall degree of sulphonation of the dye sample was less than theoretical; the naphthol-sulphonic acid component would be expected to contain less rather than more than the theoretical amount of SO_3H since the lower-substituted naphthalenes will be those preferentially isolated on salting-out during recovery; the low result was shown not to be inherent in the method of analysis.

The methods outlined may not be generally applicable. For example, non-ionic impurities may be present (these can be removed by solvent extraction before exchange) and there may be functional groups within the dye which are labile in contact with the exchanger. Modifications in the technique of selective adsorption should be possible, however, for most dyes. The technique of " mixed-bed " deionisation can give the corresponding dye acids provided that they are soluble under acid conditions.

Added in Proof.—Since this paper was prepared Deuel, Solms, and Anyas-Weisz (*Helv. Chim. Acta*, 1950, **33**, 2171) have given examples of the quantitative separation of large polymeric anions [*e.g.* poly(galactur-onic acid)] from the related monomers by methods similar to those described above.

Experimental.

The capacity of each column was determined for 0·05N-solutions—sodium chloride for the strongly acid (effluent aliquots being titrated) and strongly basic resins (the effluent being examined for chloride ions), and sodium hydroxide for the weakly acid exchangers (pH measurements showing the break-through). The capacity was also determined by carrying out a trial run with the appropriate crude dye. Ash contents were determined on effluent aliquots; or the dye was precipitated and the filtered solution examined for residual anion. The effectiveness of the base-absorbing resins was determined by pH measurements and, with some dyes on lightly coloured resins, visually, a colour change being observed at the dye/dye-alkali junction.

All ashes were sulphated; the values recorded are calculated for samples dried at 140°/15 mm.

Before analysis the solutions were filtered to remove any insoluble impurity derived from the column material.

The following details for Sky Blue FF (Colour Index No. 518) are typical of those employed for a sulphonic acid direct cotton dye. The concentrations given are probably maximal for efficient exchange; the optimum rate of flow of solution was not examined. (i) An aqueous solution (850 ml.) of the dye (*ca.* 55% pure; diluent sodium chloride, 10 g./l. = 0·084 total equiv.) was passed through a column of sulphonic acid resin (A) (length, 50 cm.; diameter, 1·95 cm.; capacity for dye acid with ash $\geqslant$1%, 0·088 equiv.) in the acid form during 4 hours. The acid effluent (inorganic acid = 0·065 equiv.) was then passed through a column of strongly basic resin (D) (length, 50 cm.; diameter 1·35 cm.; capacity, 0·075 equiv.) in the basic form during 6 hours. The dye acid, isolated on evaporation, was obtained as a bright, brassy mass, m. p. *ca.* 210° (decomp.) (Found : ash, 0·5%). Excess of N-sodium hydroxide (20 ml.) was then added, and the solution passed through a column of weakly acid resin (C) (length, 55 cm.; diameter, 1·95 cm.; the resin was regenerated in the usual way, washed, and taken to the break-through with 0·05N-sodium hydroxide, again regenerated to the break-through with 0·05N-hydrochloric acid, and finally washed with water to remove chloride and to give an effluent pH 4·5; subsequent regenerations were made with the dilute acid only). The pure dye was isolated from the effluent (pH 5·0, adjusted by 0·1N-sodium hydroxide to pH 7·0) as bright coppery lumps (Found : ash, 26·9%).

(i *a*) A similar alkaline solution of the dye acid, passed through a column of carboxylic acid resin (B), length, 25 cm.; diameter, 1·35 cm., regenerated, treated with 350 ml. of N-sodium chloride, and washed free from chloride at each regeneration, gave an effluent (pH 4·0) which yielded the dye (Found : ash, 25·5%).

(ii) The dye solution (2·5 l.; 5 g./l.) was passed through a column of strongly basic resin D [length, 100 cm.; diameter, 3·3 cm.; total capacity of column *ca.* 5·5 l. (5 g. of dye per litre)] in the basic form, and the resin (C), in series, during 5 hours. The dye was isolated from the effluent (pH 5·2, adjusted to 7·0) as before (Found : ash, 27·2%).

(iii) With acid-insoluble dyes containing much carbonate impurity the solutions were first treated with the strongly basic resin (D) and then adjusted to a pH 4 by treatment with the carboxylic acid resin (B). The liberated carbon dioxide was then removed by re-passage through resin (D).

The results of purifications of this dye are summarised in the table.

Method.	pH of final soln.	Ash, %.	Comments.
(1) Sulphonic acid resin (A); strongly basic resin (D); + NaOH (excess); weakly acid (phenolic hydroxyl groups) resin (C)	4·75	25·5	
	adj. to 7·0	26·9	—
(2) Resin (D); resin (C)	5·0	26·0	10% of $NaHCO_3$ added as diluent to crude dye in one run
	adj. to 7·0	27·2	
(3) Resin (D); carboxylic resin (B); resin (D); + NaOH (excess); resin (C)	4·2	—	+ 10% of $NaHCO_3$
	adj. to 7·0	26·0	
(4) (*a*) Prepared by method of Robinson and Mills	—	31·1	~3·5% NaOAc, calc. as Na_2SO_4
(*b*) Sample from (*a*) reground and re-extracted	—	27·7	<0·5% NaOAc
(5) Resin (D); resin (C). No exclusion of carbon dioxide	—	32·1	~6% $NaHCO_3$, calc. as Na_2SO_4
Calc. for the pure dye	—	28·6	—

Resin (A), Zeokarb 215 (Permutit Co.)
Resin (B), Zeokarb 216 ,,
Resin (C), Zeokarb 237/80 ,,
Resin (D), Deacidite F (Permutit Co.)
Resin (E), Deacidite B ,,

At 2·5 g. of pure dye per litre pH 5 represents 4—5% of unneutralised dye acid, and pH 6 represents 2% (values calc. from Fig. 2).

(iv) Pure Benzopurpurin 4B (Colour Index No. 448) was similarly obtained by method (ii) (Found: ash, 17·9. Calc. for the pure dye: ash, 19·6%). Prepared according to Robinson and Mills, the dye contained 18·8% of ash and was shown by electrometric titration to contain ~1% of sodium acetate even after repeated ethanol extractions. After further purification through resin (D) and resin (B), the ash content was 18·4%.

(v) Pure Chlorazol Fast Red (Colour Index No. 419), a carboxylic acid-substituted dye, was also obtained by method (ii) (Found: ash, 22·9. Calc. for the pure dye, ash, 22·7%). Prepared according to Robinson and Mills, the dye had 24·0% of ash.

(vi) Sodium 8-acetamido-1-hydroxy-2-phenylazonaphthalene-5-sulphonate. The crude reaction product (from 15 g. of naphthol) was precipitated with acid, filtered off, and dissolved in water (2 l.). The solution was then passed through the acid resin (A) column, as in (i), during 4 hours and through the large resin (D) column, as in (ii), during 15 minutes. The final effluent was then adjusted to pH 7·0 (Found: ash 16·7. Calc. for the pure dye: ash, 17·4%).

The author thanks Dr. T. H. Morton for his interest and advice during the course of this work, Mr. R. E. Kressman of the Permutit Co. Ltd. for his assistance and samples of hydroxylic resin, and the Directors of Messrs. Courtaulds Ltd. for permission to publish this work.

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[*Received, October 17th,* 1950.]

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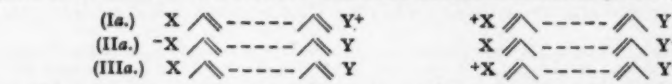
205. *Cyanine Dyes containing the Pyrrocoline Nucleus. Part I.*

By F. G. HOLLIMAN and H. A. SCHICKERLING.

A series of azadimethincyanines containing the pyrrocoline nucleus has been synthesised by the condensation of 2-substituted-3-nitroso- and -3-acetyl-1-nitroso-pyrrocolines with heterocyclic compounds containing reactive methylene groups. Light absorptions of these dyes are given and discussed.

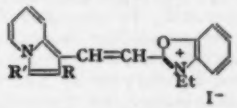
THE fundamental feature of the majority of dyes is a conjugated chain of equal numbers of double and single bonds terminated at each end by an atom which can exist in lower and higher covalency states, the difference in charge being one unit: one of the terminal atoms is in the lower, whilst the other is in the higher covalency state (I, II, III). Such an arrangement permits of resonance between the two extreme electronic structures (*a* and *b*).



The cyanine dyes conform to the structure (I) and are characterised by having nitrogen for

both terminal atoms, linked in heterocyclic systems in such a way that part of the periphery of each heterocyclic ring contributes to the conjugated system. For compounds of such a constitution, the lower, tercovalent state of the nitrogen atom demands that the heterocyclic nitrogen atoms, besides being linked in their respective ring systems, carry an additional group. The latter is present merely to provide for the bonding requirements, the bond to this group being the important feature and not the group itself; this group has, in fact, usually been methyl or ethyl. Bond requirements could, however, be satisfied in an alternative way: the additional valency to the nitrogen atom could be satisfied by a bond linking this atom to one of the atoms involved in the conjugated chain. In this way an additional ring system would be produced, the heterocyclic nitrogen atom thereby being a bridge atom between two fused ring systems. This paper records our initial experiments in preparing dyes of this type.

(IV.)



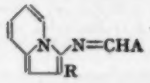
(V.)

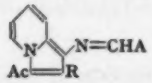
A suitable heterocyclic system for the synthesis of cyanine dyes with these characteristics is pyrrocoline (IV) (Scholtz, *Ber.*, 1912, **45**, 734). Dyes containing this nucleus have been reported only in a patent, *viz.*, cyanine dyes derived from pyrrocoline and benzoxazole (as V) (Brooker and Sprague, U.S.P. 2,409,612). Borrows, Holland, and Kenyon (*J.*, 1946, 1069 *et seq.*) recently reported that 2-substituted pyrrocolines (Tschitschibabin, *Ber.*, 1927, **60**, 1607) readily underwent nitrosation at position 3, and further that a nitroso-group could be introduced into position 1 if the more reactive 3-position was first substituted by an acetyl group. We have shown that the nitroso-group in these compounds, like that in nitrosoindoles (Mann and Haworth, *J.*, 1944, 670; Huang-Hsinmin and Mann, *J.*, 1949, 2911), can be condensed with reactive methylene groups in suitable heterocyclic systems with the production of dyes: since the five-membered ring of the pyrrocoline nucleus forms part of the conjugated system linking the two heterocyclic nitrogen atoms, the use of the 1- and the 3-nitroso-compounds provides dyes with conjugated chains of different lengths (compare VI, VIII, and X with VII, IX, and XI).

We have used the four nitroso-compounds synthesised by Borrows, Holland, and Kenyon (*loc. cit.*), *viz.* 2-methyl-3-nitroso-, 3-nitroso-2-phenyl-, 3-acetyl-2-methyl-1-nitroso-, and 3-acetyl-1-nitroso-2-phenyl-pyrrocoline, prepared essentially by the methods described by these workers, whose synthesis of 2-phenylpyrrocoline we have also adopted. For the 2-methyl compound, however, we have preferred to use the more readily prepared bromoacetone rather than chloroacetone (cf. Tschitschibabin and Stepanow, *Ber.*, 1929, **62**, 1068). In spite of the low yield (10%) recorded by Tschitschibabin (*Ber.*, 1927, **60**, 1607) for use of the bromo-compound, we have been able, by using only freshly prepared bromoacetone, by very careful temperature control during the reaction with α-picoline, and by using excess of sodium hydrogen carbonate in the cyclisation of the picolinium salt, to obtain 2-methylpyrrocoline in 61% yield.

The four nitroso-compounds have been condensed with α-picoline methiodide, quinaldine methiodide, and 2 : 3 : 3-trimethylindolenine methiodide, to give twelve azadimethincyanines (VI—XI; R = Me or Ph). A further range, with wider variation in the non-pyrrocolinyl nucleus, has been obtained by condensing 1- and 3-nitroso-2-phenylpyrrocoline with 6-ethoxy-2-methylquinoline ethiodide, 2-methyl-5 : 6-benzoquinoline methiodide, and 2-methylpyridino(2′ : 3′-5 : 6)quinoline methiodide.

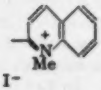
Exploratory experiments on the condensation of 2-methyl-3-nitrosopyrrocoline and α-picoline methiodide in alcoholic solution showed that the use of piperidine as catalyst was inferior to the

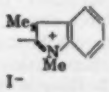
(VI, VIII, X.) 



(VII, IX, XI.)

In (VI and VII) A =

In (VIII and IX) A = 

In (X and XI) A = 

use of 0·1—0·2 molecular proportion of sodium hydroxide. This was so with regard to both the yield and the purity of the condensation product, which, when piperidine was used, appeared to

separate in the smectic state on recrystallisation. Consequently we have used aqueous sodium hydroxide in this series of condensations and have found it to be satisfactory in all but a few cases: in the preparation of 2-[(1-methylpyridine)][3-(2-phenylpyrrocoline)]-α-azadimethincyanine iodide (VI; R = Ph) reversion to the use of piperidine, the proportion of which was critical, gave better yields, and in the condensations with 2 : 3 : 3-trimethylindolenine methiodide, satisfactory results were obtained only by using alcoholic sodium hydroxide.

The yields of the condensation products are obviously subject to variation from a number of factors: the reactivities of the nitroso- and the methyl groups in the reactants; the stability of the products; and, since the dyes were obtained by direct crystallisation and collection from the reaction mixture, their solubility in the solvent used (methyl or ethyl alcohol). Some indication of the reactivities could be obtained from the time taken for the initial green colour of the reaction mixture to begin to change as the colour of the dye became superimposed on that of the nitroso-compound. In some cases, this took place even in the absence of the catalyst, in others shortly after its addition in the cold, whilst some condensations required prolonged refluxing. From condensations with the same methylene compound, it was apparent that substitution of the 2-phenyl for the 2-methyl group had little effect on the reactivity of the nitroso-group in the pyrrocoline or 3-acetylpyrrocoline series. On the other hand, the change in colour took place far more rapidly with the 3-acetyl-1-nitroso- than with the 3-nitroso-derivatives, this being particularly noticeable with the 2-phenyl derivatives where higher yields of the condensation products from the acetyl compound were isolated without refluxing being necessary. Whether this increased reactivity of the nitroso-group should be attributed to its changed position, to an activating effect of the acetyl group, or to a combination of these factors is being investigated. The yield of dye obtained from the 3-acetyl-1-nitrosopyrrocolines was invariably greater than that from the corresponding 2-substituted compound; apart from the effect due to the nitroso-group, this appears to be connected with the lower solubility of the dyes containing the acetyl substituent.

The absorption spectra, between 200 and 700 mμ., of our dyes were determined with a Beckman spectrophotometer (see table). The most outstanding feature of these is the change

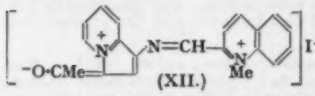
Dye.					
Pyrrocoline nucleus.*	Other nucleus.†	Solvent.	$\lambda_{max.}$.	$10^{-4}\,\varepsilon_{max.}$.	$\lambda_2 - \lambda_1$.
M-3	P	Water	544	3·77	68
AM-1	,,	,,	478	1·81	
P-3	,,	,,	548	2·76	72
AP-1	,,	,,	476	2·04	
M-3	Q	,,	596	4·05	84
AM-1	,,	,,	512	3·07	
P-3	,,	,,	600	3·40	84
AP-1	,,	,,	516	2·51	
M-3	I	Alcohol	[560]	[1·15]	30
			596	1·32	
AM-1	,,	,,	566	3·42	
P-3	,,	,,	554	1·50	− 6
AP-1	,,	,,	560	2·68	
P-3	EQ	,,	606	6·08	74
AP-1	,,	,,	532	3·84	
P-3	BzQ	,,	608	5·72	76
AP-1	,,	,,	532	3·88	
P-3	PyQ	,,	610	6·10	72
AP-1	,,	,,	538	3·52	

* M-3 = 3-(2-Methylpyrrocoline).
AM-1 = 1-(3-Acetyl-2-methylpyrrocoline).
P-3 = 3-(2-Phenylpyrrocoline).
AP-1 = 1-(3-Acetyl-2-phenylpyrrocoline).

† P = 2-(1-Methylpyridine).
Q = 2-(1-Methylquinoline).
I = 2-(1 : 3 : 3-Trimethylindolenine).
EQ = 2-(6-Ethoxy-1-methylquinoline).
BzQ = 2-(1-Methyl-5 : 6-benzoquinoline).
PyQ = 2-[1-Methylpyridino(2′ : 3′-5 : 6)quinoline].

in the wave-length and intensity of the maxima on passing from the 2-substituted 3-pyrrocolinyl nucleus to the 2-substituted 3-acetyl-1-pyrrocolinyl nucleus: for all dyes except those derived from the indolenine, this change takes the form of a decrease in the intensity together with a hypsochromic shift of *ca.* 70—80 mμ., and doubtless arises from the fact that the conjugated chain linking the two heterocyclic nitrogen atoms is longer by one $-CH{=}CH-$ group in the 3- than in the 1-pyrrocoline dyes. In the conventional type of cyanine dye, the increase in $\lambda_{max.}$ for an increase in conjugated chain length of two carbon atoms is about 100 mμ. (Brooker, Sprague, Smythe, and Lewis, *J. Amer. Chem. Soc.*, 1940, **62**, 1116), and the fact that, in our

compounds, the shift in $\lambda_{max.}$ is some 20—30 mμ. less may be due to the fact that the dyes with the shorter chain have an acetyl group present in position 3. It is likely that the presence of this group allows such forms as (XII) to contribute to the resonance state, and, whereas the shortening of the conjugated chain leads to the observed hypsochromic shift, the additional resonance arising from the presence of the acetyl group might well lead to a partially neutralising bathochromic effect. With such resonance possibilities with the acetyl group, the 2-substituted 3-acetyl-1-pyrrocoline dyes bear a certain resemblance to the merocyanins (cf. Mees, " The Theory of the Photographic Process," New York, 1942, p. 1035).



(XII.)

The case of the indolenine compounds is anomalous : in both the 2-methyl- and the 2-phenylpyrrocoline pairs, the change from the 3-pyrrocoline to the 3-acetyl-1-pyrrocoline system produces an increase in absorption intensity. Furthermore, with the 2-methylpyrrocoline compounds the hypsochromic effect of shortening the conjugated chain is reduced to only 30 mμ., whilst with the 2-phenylpyrrocoline-indolenine dyes, the effect is reversed, shortening of the chain leading to a bathochromic effect of 6 mμ. In view of these anomalies, we have attempted, for comparison, to synthesise analogous dyes by condensation of the nitrosopyrrocolines with 2-methylbenzthiazole methiodide and 2-methylbenzoxazole ethiodide. Although both 2-methyl-3-nitroso- and 3-acetyl-2-methyl-1-nitroso-pyrrocoline thus gave intense colours with 2-methylbenzthiazole methiodide in boiling alcohol in the presence of sodium hydroxide, a dye was only obtained from the acyl pyrrocoline. With 2-methylbenzoxazole ethiodide and 3-nitroso-2-phenylpyrrocoline, no colour change could be induced; the more reactive 3-acetyl-1-nitroso-2-phenylpyrrocoline caused a slow colour change but no dye could be isolated. This failure to effect condensation between nitrosopyrrocolines and 2-methylbenzoxazole ethiodide is interesting in view of Mann and Haworth's failure (*J.*, 1944, 670) to condense their nitrosoindoles with the same reactive methylene compound.

Experimental.

(M. p.s are uncorrected.)

" Dry alcohol " refers to solvent which has been dried by refluxing with sodium and ethyl phthalate before fractionation.

2-Methylpyrrocoline (cf. Tschitschibabin, *Ber.*, 1927, **60**, 1614).—α-Picoline (20 g.), thoroughly chilled in ice-water, was treated with bromoacetone (*Org. Synth.*, **10**, 12) (30 g., 1 mol.) with swirling. The mixture was removed from the cooling bath, but was replaced therein immediately it showed signs of becoming warm. By such continued control, the reaction was allowed to proceed, without the temperature rising appreciably, until the mixture had become a thick, viscous syrup. This was set aside at room temperature during 3 hours, by which time it had crystallised. A solution of the picolinium salt in water (240 c.c.) was extracted with ether (80 c.c.) and, after treatment with sodium hydrogen carbonate (40 g.), was heated under reflux on a water-bath; the temperature of the bath was slowly raised to boiling and held there for 2 hours. Steam-distillation of the mixture then gave 2-methylpyrrocoline which was dried in air. 17·6 G. (61%) were obtained, of m. p. 59·5° unchanged on sublimation.

3-Nitroso-2-phenylpyrrocoline.—Some modification and amplification of the method of Borrows, Holland, and Kenyon (*J.*, 1946, 1076) is recorded. 2-Phenylpyrrocoline (*idem, ibid.*) (12·5 g.) was dissolved in concentrated hydrochloric acid (40 c.c.), and the solution diluted at 35° with water (80 c.c.). A solution of sodium nitrite (6·25 g., 1·5 mols.) in water (33 c.c.) was added dropwise, with stirring, the temperature being kept at 35°. The orange-red precipitate began to form when most of the nitrite had been added. After 1 hour at room temperature the thick magma was filtered off. The solid was dissolved in water (1 l.), the solution cooled to 40°, and solid sodium hydrogen carbonate carefully added with stirring, until some carbonate remained undissolved; this excess was then brought into solution by careful heating (> 80°). On slow cooling with continual stirring, the green nitroso-compound gradually crystallised from the emulsion and was filtered off after 10 minutes at 0°. The original filtrate from the reaction mixture was worked up in the same way and the combined lots of 3-nitroso-2-phenylpyrrocoline were recrystallised from 50% aqueous alcohol, to give 10 g. (70%) of m. p. 98—99° (Borrows, Holland, and Kenyon report m. p. 97·5—98°).

[2-(1-Methylpyridine)][3-(2-methylpyrrocoline)]-α-azadimethincyanine Iodide (VI; R = Me).—A solution of 2-methyl-3-nitrosopyrrocoline (*idem, ibid.*) (1 g.), α-picoline methiodide (1·47 g., 1 mol.), and 5% aqueous sodium hydroxide (0·5 c.c., 0·1 mol.) in alcohol (30 c.c.) was refluxed, a crystalline precipitate rapidly being produced. After 2 hours, the mixture was cooled and the solid collected. Recrystallisation from water gave fine black needles of the *azacyanine* (44·5%), m. p. 262—263° (decomp.) (Found : C, 50·4; H, 4·1. $C_{16}H_{16}N_2I$ requires C, 50·9; H, 4·2%).

[2-(1-Methylpyridine)][3-(2-phenylpyrrocoline)]-α-azadimethincyanine Iodide (VI; R = Ph).—(*a*) 3-Nitroso-2-phenylpyrrocoline (1 g.) and α-picoline methiodide (1·06 g., 1 mol.) in alcohol (15 c.c.) were treated with 5% aqueous sodium hydroxide (0·8 c.c., 0·2 mol.), the colour of the solution immediately changing from green to scarlet. After 6 hours' boiling, the solution was cooled. The crystalline solid deposited was recrystallised from water, giving the greenish-brown *azacyanine* (11·5%), m. p. 212—213° (decomp.) (Found : C, 57·3; H, 4·2. $C_{21}H_{19}N_2I$ requires C, 57·4; H, 4·1%).

(*b*) The same weights of the nitroso-compound and the methiodide in alcohol (20 c.c.) were treated with piperidine (0·2 g., 0·5 mol.). The mixture was refluxed and after 5—10 minutes began to change colour. After 5·5 hours' boiling, cooling gave 0·16 g. (8·5%) of the *cyanine*. Addition of a further quantity of piperidine (0·2 g., 0·5 mol.) and further refluxing gave an additional quantity of the dye (0·18 g.), but further increase in the proportion of piperidine was unsuccessful. Recrystallisation from water gave brown crystals m. p. 212—213° (decomp.) unchanged on admixture with the product from (*a*) (Found: C, 57·2; H, 4·1%).

[2-(1-*Methylpyridine*)][1-(3-*acetyl*-2-*methylpyrrocoline*)]-α-*azadimethincyanine Iodide* (VII; R = Me).—3-Acetyl-2-methyl-1-nitrosopyrrocoline (*idem*, *ibid.*) (0·5 g.), and α-picoline methiodide (0·58 g., 1 mol.) in alcohol (18 c.c.) treated with 5% aqueous sodium hydroxide (0·25 c.c., 0·1 mol.) gave an immediate dark red, crystalline precipitate. After 10 minutes, this *dye* was collected (0·62 g., 60%) and recrystallised from water, forming dark, brownish-red needles, m. p. 243—235° (decomp.) (Found: C, 51·0; H, 4·3. $C_{18}H_{18}ON_2I$ requires C, 51·6; H, 4·3%). Refluxing the filtrate from the reaction mixture failed to yield a further quantity of dye.

[2-(1-*Methylpyridine*)][1-(3-*acetyl*-2-*phenylpyrrocoline*)]-α-*azadimethincyanine Iodide* (VII; R = Ph).—3-Acetyl-1-nitroso-2-phenylpyrrocoline (*idem*, *ibid.*) (1 g.) and α-picoline methiodide (0·82 g., 1 mol.), dissolved in alcohol (20 c.c.), were treated with 5% sodium hydroxide solution (0·3 c.c., 0·1 mol.) which caused an immediate change in colour from green to red. After 6 hours' boiling, cooling of the solution gave a crystalline precipitate (0·92 g., 50%), m. p. 211—212° (decomp.). Recrystallisation from water gave golden-brown needles of the *hydrate* of unchanged m. p. (Found: C, 55·2, 55·0; H, 4·5, 4·5; loss in wt. at 100°/15 mm. during 2 hours, 3·7%. $C_{23}H_{23}ON_2I,H_2O$ requires C, 55·3; H, 4·4%; H_2O, 3·6%).

[3-(2-*Methylpyrrocoline*)][2-(1-*methylquinoline*)]-α-*azadimethincyanine Iodide* (VIII; R = Me).—2-Methyl-3-nitrosopyrrocoline (1 g.) and quinaldine methiodide (1·78 g., 1 mol.) in methyl alcohol (30 c.c.) with 5% sodium hydroxide solution (0·5 c.c., 0·1 mol.) were refluxed. Solid separated and after 5·5 hours the solution was cooled and the solid *salt* collected (1·24 g., 46%). Two recrystallisations from water gave dark green needles, m. p. 252—253° (decomp.) (Found: C, 56·3; H, 4·4. $C_{20}H_{18}N_2I$ requires C, 56·2; H, 4·2%).

[3-(2-*Phenylpyrrocoline*)][2-(1-*methylquinoline*)]-α-*azadimethincyanine Iodide* (VIII; R = Ph).—A solution of 3-nitroso-2-phenylpyrrocoline (1 g.) and quinaldine methiodide (1·28 g., 1 mol.) in alcohol (30 c.c.) was treated with 5% aqueous sodium hydroxide and refluxed for 8 hours. The solid *iodide* separating was removed after 3, 6, and 8 hours, giving a total of 1·13 g. (51%). Recrystallisation (10% aqueous alcohol) gave dark reddish-brown needles, m. p. 226—228° (decomp.) (Found: C, 61·4; H, 4·3. $C_{25}H_{23}N_2I$ requires C, 61·4; H, 4·1%).

[1-(3-*Acetyl*-2-*methylpyrrocoline*)][2-(1-*methylquinoline*)]-α-*azadimethincyanine Iodide* (IX; R = Me).—3-Acetyl-2-methyl-1-nitrosopyrrocoline (0·5 g.) and quinaldine methiodide (0·71 g., 1 mol.) in alcohol (25 c.c.) treated with 5% aqueous sodium hydroxide (0·25 c.c., 0·1 mol.) gave an immediate colour change, accompanied by the deposition of crystals. After 2 minutes' boiling, the mixture was cooled and the solid collected (0·8 g., 68%). Recrystallisation (water) gave brownish-red needles of the *cyanine iodide dihydrate*, m. p. 222—223° (decomp.) (Found: C, 53·0, 52·8; H, 4·9, 4·6; loss in weight at 100°/15 mm. during 2 hours, 6·6. $C_{22}H_{23}ON_2I,2H_2O$ requires C, 52·3; H, 4·7; H_2O, 7·1%).

[1-(3-*Acetyl*-2-*phenylpyrrocoline*)][2-(1-*methylquinoline*)]-α-*azadimethincyanine Iodide* (IX; R = Ph).—Refluxing a solution of 3-acetyl-1-nitroso-2-phenylpyrrocoline (1 g.) and quinaldine methiodide (1·08 g., 1 mol.) in alcohol (20 c.c.) caused a change in colour to greenish-red. Further change to reddish-violet was produced upon the addition of 5% sodium hydroxide solution (0·4 c.c., 0·13 mol.), and refluxing induced rapid precipitation of golden-brown crystals. The mixture was cooled after 2 hours' refluxing and the cyanine iodide collected (1·44 g., 79%). It recrystallised from water as the *monohydrate*, golden-brown platelets, m. p. 214—215° (decomp.) (Found: C, 59·6, 59·3; H, 4·3, 4·2; loss in weight at 100°/15 mm. during 2 hours, 3·07. $C_{27}H_{23}ON_2I,H_2O$ requires C, 59·0; H, 4·4; H_2O, 3·27%).

[3-(2-*Methylpyrrocoline*)][2-(1 : 3 : 3-*trimethylindolenine*)]-α-*azadimethincyanine Iodide* (X; R = Me).—A solution of 2-methyl-3-nitrosopyrrocoline (0·30 g.) and 2 : 3 : 3-trimethylindolenine methiodide (0·57 g., 1 mol.) in dry alcohol (12 c.c.) was treated with 5% alcoholic sodium hydroxide (0·30 c.c., 0·2 mol.) and refluxed. The colour changed slowly to deep purple in the first 2 hours, but no solid separated. After 7 hours the mixture was chilled but yielded no solid. Concentration and storage at 0° finally gave 0·12 g. (14·3%) of deep purple crystals which, recrystallised from alcohol, had m. p. 186—189° (decomp.) (Found: C, 57·0; H, 4·9. $C_{21}H_{23}N_2I$ requires C, 56·9; H, 5·0%).

With aqueous sodium hydroxide in place of the alcoholic reagent the *cyanine* was obtained in somewhat lower yield (10·7%).

[3-(2-*Phenylpyrrocoline*)][2-(1 : 3 : 3-*trimethylindolenine*)]-α-*azadimethincyanine Iodide* (X; R = Ph).—3-Nitroso-2-phenylpyrrocoline (0·4 g.) and 2 : 3 : 3-trimethylindolenine methiodide (0·54 g., 1 mol.) in solution in dry alcohol (12 c.c.) were treated with 5% alcoholic sodium hydroxide (0·29 c.c., 0·2 mol.). Change in colour to blue only took place slowly on refluxing which was continued for 6 hours. The cyanine iodide (0·34 g., 37·5%) separated at 0° during 3 days and was recrystallised from alcohol, to give the *trihydrate* as purple needles, m. p. 249—250° (Found: C, 55·6; H, 5·1; loss in weight at 100°/15 mm. during 2 hours, 9·4. $C_{28}H_{34}N_2I,3H_2O$ requires C, 55·8; H, 5·3; H_2O, 9·6%).

The use of aqueous alkali as the catalyst in this condensation led to the production of the desired dye, but in lower yield (33·1%). Piperidine, on the other hand, only succeeded in producing a slight colour change in the reaction mixture during some 7 hours' refluxing.

[1-(3-*Acetyl*-2-*methylpyrrocoline*)][2-(1 : 3 : 3-*trimethylindolenine*)]-α-*azadimethincyanine Iodide* (XI; R = Me).—3-Acetyl-2-methyl-1-nitrosopyrrocoline (0·3 g.) and 2 : 3 : 3-trimethylindolenine methiodide (0·45 g., 1 mol.) in dry alcohol (10 c.c.) with 5% alcoholic sodium hydroxide (0·25 c.c., 0·2 mol.) was

refluxed during 6 hours: a gradual change in colour to red took place in the first 2 hours. The solid (0·16 g., 22%) separating overnight was recrystallised from alcohol, to give golden-brown crystals of the *azacyanine*, m. p. 203—205° (decomp.) (Found: C, 54·2, 54·2; H, 4·9, 4·8. $C_{23}H_{24}ON_3I,H_2O$ requires C, 54·8; H, 5·2%).

Aqueous alkali was unsatisfactory, giving only a 3% yield.

[1-(3-*Acetyl*-2-*phenylpyrrocoline*)][2-(1 : 3 : 3-*trimethylindolenine*)]-α-*azadimethincyanine Iodide* (XI; R = Ph).—Heating 3-acetyl-1-nitroso-2-phenylpyrrocoline (0·40 g.) with the indolenine methiodide (0·46 g., 1 mol.) in dry alcohol (10 c.c.) caused the development of a purple colour in the initially green solution. The addition of 5% alcoholic sodium hydroxide (0·24 c.c., 0·2 mol.) increased the rate of colour change and the mixture was then refluxed for 7 hours. Solid soon began to separate and more crystallised on cooling. Next morning the dye was collected (0·25 g., 30%) and recrystallised from alcohol as golden-brown crystals of the *monohydrate*, m. p. 226—228° (Found: C, 59·0; H, 4·9; loss in weight at 100°/15 mm. for 2 hours, 3·7. $C_{23}H_{24}ON_3I,H_2O$ requires C, 59·4; H, 4·9; H_2O, 3·2%).

Both aqueous alkali and piperidine gave a marked colour change; with the former a low yield (16%) of dye was obtained whilst with the latter only unchanged pyrrocoline could be isolated.

[3-(2-*Phenylpyrrocoline*)][2-(6-*ethoxy*-1-*ethylquinoline*)]-α-*azadimethincyanine Iodide*.—3-Nitroso-2-phenylpyrrocoline (0·39 g.) and 6-ethoxy-2-methylquinoline ethiodide (0·60 g., 1 mol.) in alcohol (10 c.c.) were treated with 5% aqueous sodium hydroxide (0·27 c.c., 0·2 mol.). The colour of the boiling solution slowly changed to blue. After 7 hours the solution was cooled and set aside overnight, yielding 0·38 g. (40%) of dark green crystals which recrystallised from 50% aqueous alcohol, as prisms of the *hemihydrate*, m. p. 187° (decomp.) (Found: C, 59·9, 60·0; H, 4·6, 4·8; loss in weight at 100°/15 mm. during 2·5 hours, 1·8. $C_{25}H_{24}ON_3I,\frac{1}{2}H_2O$ requires C, 60·4; H, 4·8; H_2O, 1·6%).

[1-(3-*Acetyl*-2-*phenylpyrrocoline*)][2-(6-*ethoxy*-1-*ethylquinoline*)]-α-*azadimethincyanine Iodide*.—Addition of 5% aqueous sodium hydroxide (0·27 c.c., 0·2 mol.) to a solution of 3-acetyl-1-nitroso-2-phenylpyrrocoline (0·46 g.) and 6-ethoxy-2-methylquinoline ethiodide (0·60 g., 1 mol.) in alcohol (10 c.c.) produced an immediate change in colour to deep purple. Crystallisation of the condensation product took place during refluxing, which was continued during 6 hours. After 12 hours at room temperature, the golden-brown dye was collected (0·77 g., 74·7%) and recrystallised from 33% aqueous alcohol, giving fine needles of a *hydrate*, m. p. 211° (decomp.) (Found: C, 57·7, 58·3; H, 4·8, 5·0; loss in weight at 100°/15 mm. during 2·5 hours, 4·1. $C_{25}H_{24}O_2N_3I,1\frac{1}{2}H_2O$ requires C, 58·5; H, 5·0; H_2O, 4·1%).

[3-(2-*Phenylpyrrocoline*)][2-(1-*methyl*-5 : 6-*benzoquinoline*)]-α-*azadimethincyanine Iodide*.—3-Nitroso-2-phenylpyrrocoline (0·26 g.) and 2-methyl-5 : 6-benzoquinoline methiodide (0·40 g., 1 mol.), dissolved in methyl alcohol (23 c.c.), were treated with 5% sodium hydroxide solution (0·19 c.c., 0·2 mol.), and the mixture refluxed. A colour change to deep green soon took place, and after 3 hours solid began to separate. After 6·5 hours, the mixture was cooled and set aside overnight before the *iodide* (0·32 g., 50%) was collected and recrystallised (water, 10% aq. alcohol) to give dark green prisms, m. p. 205° (decomp.) (Found: C, 65·2; H, 4·2. $C_{29}H_{23}N_3I$ requires C, 64·7; H, 4·1%).

[1-(3-*Acetyl*-2-*phenylpyrrocoline*)][2-(1-*methyl*-5 : 6-*benzoquinoline*)]-α-*azadimethincyanine Iodide*.—A solution of 3-acetyl-1-nitroso-2-phenylpyrrocoline (0·24 g.) and 2-methyl-5 : 6-benzoquinoline methiodide in methyl alcohol (15 c.c.) was treated with 5% sodium hydroxide solution (0·14 c.c., 0·2 mol.), whereupon an immediate colour change to brownish-red and separation of solid took place. After 7 hours' boiling, the mixture was cooled and set aside overnight, to yield 0·30 g. (58%) of the *azacyanine iodide*, recrystallisation of which from 40% aqueous alcohol gave reddish-brown needles, m. p. 231° (decomp.) (Found: C, 63·8; H, 3·7. $C_{31}H_{24}ON_3I$ requires C, 64·0; H, 4·1%).

[3-(2-*Phenylpyrrocoline*)][2-(1-*methylpyridino*(2′ : 3′-5 : 6)*quinoline*)]-α-*azadimethincyanine Iodide*.—3-Nitroso-2-phenylpyrrocoline (0·33 g.) and 2-methylpyridino(2′ : 3′-5 : 6)quinoline methiodide (0·50 g., 1 mol.) in methyl alcohol (25 c.c.) with 5% sodium hydroxide solution (0·24 c.c., 0·2 mol.) rapidly deposited crystals on refluxing. After 5 hours, the mixture was cooled and set aside overnight, then yielding 0·28 g. (35%) of dark green crystals. Recrystallisation from 40% aqueous alcohol gave flat triangular crystals of the *azacyanine iodide*, m. p. 215° (decomp.) (Found: C, 62·0; H, 3·8. $C_{34}H_{31}N_4I$ requires C, 62·2; H, 3·9%).

[1-(3-*Acetyl*-2-*phenylpyrrocoline*)][2-(1-*methylpyridino*(2′ : 3′-5 : 6)*quinoline*)]-α-*azadimethincyanine Iodide*.—3-Acetyl-1-nitroso-2-phenylpyrrocoline (0·39 g.) and 2-methylpyridino(2′ : 3′-5 : 6)quinoline methiodide (0·50 g., 1 mol.) in methyl alcohol (25 c.c.), treated with 5% aqueous sodium hydroxide (0·24 c.c., 0·2 mol.), gave an immediate precipitate with a colour change to deep reddish-brown. After 5 hours' refluxing and then setting aside overnight, the *azacyanine iodide* was collected (0·70 g., 81%). Owing to its very slight solubility the dye could not be recrystallised (Found: C, 61·2; H, 3·9. $C_{32}H_{29}ON_4I$ requires C, 61·8; H, 3·9%).

[1-(3-*Acetyl*-2-*methylpyrrocoline*)][2-(3-*methylbenzthiazole*)]-α-*azadimethincyanine Iodide*.—3-Acetyl-2-methyl-1-nitrosopyrrocoline (0·42 g.) and 2-methylbenzthiazole methiodide (0·60 g., 1 mol.) in methyl alcohol (8 c.c.), on warming, gave a precipitate of a dark solid. Methyl alcohol (7 c.c.) and 5% alcoholic sodium hydroxide (0·33 c.c., 0·2 mol.) were adde dand the mixture was refluxed for 5·5 hours. Next morning the brown crystals (0·66 g., 67%) were collected and washed with alcohol and then ether. Recrystallisation was difficult and was accomplished from nitromethane to yield a *hydrate* as clusters of needles, m. p. 246·5—247·5° (Found: C, 49·3; H, 3·8; loss in weight at 100°/15 mm. during 30 minutes, 2·5. $C_{20}H_{16}ON_3IS,\frac{1}{2}H_2O$ requires C, 49·3; H, 4·0; H_2O, 2·5%).

Attempted Condensation of 2-*Methyl*-3-*nitrosopyrrocoline and* 2-*Methylbenzthiazole Methiodide*.—The nitroso-compound (0·33 g.) and the methiodide (0·60 g., 1 mol.) in methyl alcohol (8 c.c.) with 5% alcoholic sodium hydroxide solution (0·33 c.c., 0·2 mol.) were refluxed during 6 hours. Almost immediately, the colour of the mixture darkened, and dark crystals began to separate. The solid (0·16 g.) was collected after 12 hours at room temperature and washed with alcohol, then with ether. The

product proved very difficult to recrystallise: alcohol-extraction gave a soluble fraction which proved not to be the desired dye (Found: C, 56·2; H, 4·6. Calc. for $C_{18}H_{14}N_2IS$: C, 49·9; H, 3·7%).

Attempted Condensation of 3-Nitroso-2-phenylpyrrocoline with 2-Methylbenzoxazole Ethiodide.—The nitroso-compound (0·38 g.) and the ethiodide (0·50 g., 1 mol.) in alcohol (12 c.c.) with 5% aqueous sodium hydroxide (0·27 c.c., 0·2 mol.) were refluxed for 7 hours during which a greenish-brown solid separated; apart from this no colour change was noticed. The solid separating later was unchanged ethiodide.

Use of piperidine (1 mol.) in place of sodium hydroxide gave no colour change and no solid was isolated.

Attempted Condensation of 3-Acetyl-1-nitroso-2-phenylpyrrocoline with 2-Methylbenzoxazole Ethiodide.—Refluxing a solution of the nitroso-compound (0·12 g.) and the ethiodide (0·13 g., 1 mol.) in alcohol (5 c.c.) with 5% sodium hydroxide solution (0·07 c.c., 0·2 mol.) produced a very slow colour change to deep bluish-green during 6 hours. Only unchanged nitroso-compound was isolated.

Photographic Properties of the Dyes (VI—IX; R = Me or Ph).—These dyes have been tested for photographic properties in the laboratories of Messrs. Kodak, Ltd., who report that when the dyes were added to emulsions of various types desensitisation and loss of contrast were caused in all cases. Furthermore they were ineffective as backing dyes for photographic plates.

We thank Messrs. Kodak, Ltd., for their tests upon some of the dyes and Imperial Chemical Industries Limited, Dyestuffs Division, for gifts of some heterocyclic compounds.

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206. *The Absorption Spectrum of Keten in the Far Ultra-violet.*

By W. C. PRICE, J. P. TEEGAN, and A. D. WALSH.

The absorption spectrum of keten has been photographed in the far ultra-violet. Between 1830 and 1300 A. it bears a certain resemblance to that of ethylene, shown in (*a*) the vibrational patterns of the successive electronic states, (*b*) the proportionate reduction of the vibrational frequencies of the excited states from the ground state values, and (*c*) the term values of corresponding bands that are Rydberg in type. A Rydberg series leading to a limit of 9·60(5) ± 0·02 v. has been found: it arises from the excitation of an electron from a π-orbital localised in the C–C bond. The considerable decrease in first ionisation potential relative to ethylene is mainly caused by a particular stability of the higher excited states and of $(CH_2{:}CO)^+$. This is explicable by the assumption of conjugation between the π-C:C and the 2pπ-O orbitals in the excited states and in $(CH_2{:}CO)^+$, *i.e.*, the tendency of the 2pπ-O electrons to occupy the place vacated in the C:C-π-orbital. Stabilisation of the ground state by conjugation between the bonding π-C:C and non-bonding 2pπ-O orbitals appears to be small in comparison with that of the excited and the ionic states arising from this cause.

A transition caused by excitation of an electron in the CO group of the molecule occurs between 2150 and 1950 A.

PREVIOUS studies have been made of the spectra, in the far ultra-violet, of ethylene (Price and Tutte, *Proc. Roy. Soc.*, 1940, *A*, **174**, 207) and carbon dioxide (Price and Simpson, *ibid.*, 1939, *A*, **169**, 501). The present paper reports a study of the spectrum of keten, which is closely related to ethylene and is isoelectronic with carbon dioxide.

Experimental.—Our plates were obtained with a 1-m. normal incidence spectrograph, the grating being of glass with *ca.* 30,000 lines to the inch, giving a dispersion of *ca.* 8 A./mm. The large volume of the spectrograph (*ca.* 40 l.) minimised absorption by the products of photodecomposition, the accumulation of which was prevented by continuously pumping the material through the system: our plates showed no strong absorption due to either ethylene or carbon monoxide.

The keten was kindly provided by Professor G. Herzberg. It had been freshly prepared by pyrolysis of acetone and was purified by distillation *in vacuo*.

Description of the Spectrum.—In the near ultra-violet region, the absorption spectrum of keten consists of diffuse bands between 3850 and 2607 A. (Lardy, *J. Chim. physique*, 1924, **21**, 353). This represents a shift of about 200 A. to long wave-lengths relative to the corresponding bands in ketones. There are no sharp bands in this region, and the molecule exhibits no fluorescence (Norrish, Crone, and Saltmarsh, *J.*, 1933, 1533; *J. Amer. Chem. Soc.*, 1934, **56**, 1644).

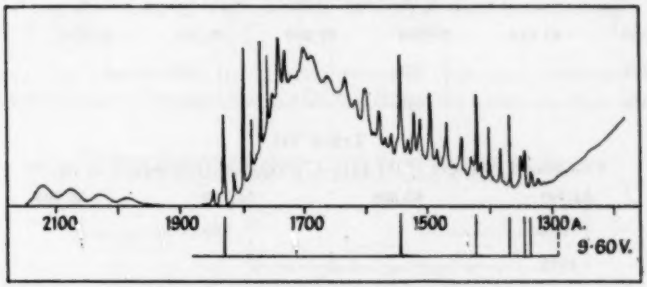
Approaching the far ultra-violet region from the long wave-length end, the spectrum begins

with four diffuse bands in the region 2150—1950 A. (Fig. 1). These occur at higher pressures than are necessary to bring out the bands at shorter wave-lengths reported below, and the system appears to be analogous to that occurring in aldehydes and ketones in the 2000—1600-A. region. The four bands have a frequency separation of ~1100 cm.$^{-1}$ ($_1\Delta_2 \sim 1093$ cm.$^{-1}$; $_2\Delta_3 \sim 1093$ cm.$^{-1}$; $_3\Delta_4 \sim 1170$ cm.$^{-1}$). It is unlikely that this represents a parallel-type vibration of the C:CO chain similar to the frequency appearing in the 1745—1600-A. absorption of ethylene, for the only plausible ground-state fundamental vibration of this type in keten has a frequency of 1120 cm.$^{-1}$ and, to judge by the ethylene spectrum, one would expect a considerably greater reduction of this in the excited state than from 1120 to ~1100 cm.$^{-1}$. There is little doubt that the 1100-cm.$^{-1}$ band corresponds to the frequency of *ca.* 1200 cm.$^{-1}$ found in the 1820—1650-A. region for acetaldehyde (Walsh, *Proc. Roy. Soc.*, 1946, *A*, **185**, 176) and in the 1960—1850-A. region for acetone (Lawson and Duncan, *J. Chem. Physics*, 1944, **12**, 329). In the latter case there is evidence that it represents the totally symmetrical hydrogen-bending frequency of the CH_3 group, which is 1357 cm.$^{-1}$ in the ground state. Similar frequencies occurring in the spectra of the methyl halides can be assigned unequivocally to similar CH bending vibrations (Price, *ibid.*, 1936, **4**, 1939). Thus the 1100-cm.$^{-1}$ separation of keten most probably represents the symmetrical CH deformation frequency which has been assigned the value 1386 cm.$^{-1}$ in the ground state (Halverson and Williams, *ibid.*, 1947, **15**, 552).

At shorter wave-lengths there appears a strong continuum of absorption with its maximum at *ca.* 1700 A.* The long-wave-length side of this is overlapped by a number of discrete bands

FIG. 1.

The far ultra-violet spectrum of keten.



(*Note : absorption intensities are qualitative.*)

starting at 1830 A. and proceeding to shorter wave-lengths. The strongest band is at 1802 A. The whole pattern, especially the occurrence of the bands in pairs, bears a considerable resemblance to that of the 1745-A. transition of ethylene.

The bands at 1830, 1802, and 1792 A. are sharp on their short-wave sides and degrade to long wave-lengths. Similarly, the ethylene 1745—1600-A. bands are degraded to the red; but, in contrast, the acetaldehyde 1800-A. bands are degraded to short wave-lengths. Table I shows the frequencies of the main bands of the keten 1830—1730-A. region. The pairs of bands lie *ca.* 860 cm.$^{-1}$ apart, the members of each pair being separated by *ca.* 300 cm.$^{-1}$. The separation of consecutive pairs in ethylene is *ca.* 1370 cm.$^{-1}$, this representing the totally symmetrical valence frequency of the C:C bond reduced from its value of 1623 cm.$^{-1}$ in the ground state. The corresponding valence frequencies of the C:CO chain in the ground state of keten are 1120 and 2153 cm.$^{-1}$ (Halverson and Williams, *loc. cit.*). It appears fairly certain that it is the 1120-cm.$^{-1}$ frequency which is concerned here. The reduction of this to *ca.* 860 cm.$^{-1}$ is, proportionately, about the same as the corresponding reduction for ethylene. The members of the pairs of bands in the ethylene spectrum are separated by 470 cm.$^{-1}$. This separation was interpreted originally as one quantum (Price and Tutte, *loc. cit.*) and later two quanta (Mulliken, *Rev. Mod. Physics*, 1942, **14**, 265) of a twisting vibration of the CH_2 groups thought to be 825 cm.$^{-1}$ in the ground state. The spectrum of deuteroethylene shows that for ethylene it is a vibration mainly involving motion of the hydrogen atoms. An equally plausible interpretation

* There is a possibility that in part the continuous absorption between 1800 and 1550 A. is due to water vapour, since (*a*) water vapour has a continuum of absorption in this region, and (*b*) bands on our plates at less than 1250 A. look like those of water vapour at these wave-lengths.

of the vibration is that it represents two quanta of the $H_2C{:}C$ bending vibration (949·2 cm.$^{-1}$ in the ground state). This would also be equivalent to a totally symmetrical vibration which is the necessary condition for it to appear in absorption from a vibrationless ground state. The only ground-state frequency of the keten molecule to which the separation of 300 cm.$^{-1}$ in the excited state could correspond seems to be two quanta of a bending vibration of the $C{:}CO$ chain. If the molecule had cylindrical symmetry, there would be two degenerate vibrations of this type. The presence of the hydrogen atoms removes this degeneracy and results in two frequencies of rather similar magnitude. In the ground state these have been assigned the values 529 and 588 cm.$^{-1}$ (Halverson and Williams, *loc. cit.*). If the 300-cm.$^{-1}$ separation represents two quanta of one of these, the reduction is, proportionately, about the same as for ethylene.

Several rather diffuse bands occur in the region 1630—1550 A. They lie within the short-wave part of the 1700-A. continuum and also on the short-wave side of it. The main bands are

TABLE I.

Separations of bands in the 1830—1730-A. *region* (*frequencies in cm.*$^{-1}$).

54,680	55,058	55,510	55,810	56,370	56,642	57,347
	378		300		272	
	830		860		977	

TABLE II.

Separations of bands in the 1630—1550-A. *region* (*frequencies in cm.*$^{-1}$).

61,550	61,844	62,369	62,900	63,364	63,914	64,365
	494		531		550	
	1019		995		1001	

TABLE III.

Vibrational structure of the 1545-A. *transition* (*frequencies in cm.*$^{-1}$).

64,760	65,368	65,785	66,395
	608		610
	1025		

TABLE IV.

Vibrational structure of the 1493-A. *transition* (*frequencies in cm.*$^{-1}$).

66,984	67,611	68,009	68,749	69,094	69,704
	627		740		610
	1025		1085		

TABLE V.

Vibrational structures of the 1421-A. (70,371 *cm.*$^{-1}$) *and* 1370-A. (72,983 *cm.*$^{-1}$) *systems.*

70,371	70,963	71,394	72,064	72,466	72,983	73,594	73,993	74,604
	592		670			611		611
	1023		1072			1010		

separated by ~1000 cm.$^{-1}$ with weaker bands ~500 cm.$^{-1}$ to the short-wave side of each. Table II records the separations observed. It is suggested below that these two frequencies are due to the same modes of vibration as are responsible for the long and the short spacing of the 1830-A. system (*i.e.*, probably a valence vibration of the $C{=}CO$ group and two quanta of a bending vibration of this group, respectively).

At 1545 A. a strong band initiates another electronic transition. The frequencies of the vibrational bands of this are recorded in Table III. A moderately strong band at 1493 A. appears to start a further electronic transition. In both cases (Tables III and IV) the frequencies involved appear to be *ca.* 1025 and *ca.* 620 cm.$^{-1}$. A similar vibration pattern appears in further

transitions starting at 1421 and 1370 A. Table V records some of the structure of these transitions.

The similarity of pattern between these successive systems indicates that similar electronic transitions are involved. The frequencies of this pattern maintain their magnitudes in the successive higher states. This in turn means that the upper orbitals of the 1545-, 1493-, 1421-, and 1370-A. transitions are all so large compared with the molecular dimensions (see Fig. 2, discussed later) that further excitation makes no difference to the binding between the atoms of the molecule. These transitions are clearly Rydberg transitions and they show the crowding together and the diminution in intensity as one passes towards shorter wave-lengths that are characteristic of such bands. They eventually fuse into a continuum of absorption just below 1300 A. and it is clear that an ionisation potential of the molecule occurs at about this wave-length. It is in fact possible to pick out the members of a Rydberg series represented by the formula

$$\nu_0^v = 77{,}491 - \frac{R}{(n - 1{\cdot}07)^2}, \quad n = 3, 4, 5 \ldots \ldots \ldots \quad (1)$$

Table VI records the observed and calculated frequencies of the members.

TABLE VI.

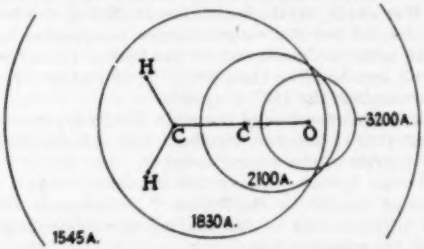
The observed and calculated frequencies of the Rydberg bands of series (1).

n.	$\nu_{obs.}$, cm.$^{-1}$.	$\nu_{calc.}$, cm.$^{-1}$.	ν ethylene, cm.$^{-1}$.	ν ethylene $-$ ν keten, cm.$^{-1}$.
3	54,680	48,039	57,340	2660
4	64,760	64,710	71,790	7030
5	70,371	70,388	77,600	7229
6	72,983	72,975	80,215	7232
7	74,367	74,371	81,625	7258
8	75,179	75,206		

Discussion.—The limit of series (1) is $9{\cdot}60(5) \pm 0{\cdot}02$ v. The series obviously corresponds to the main series found in the spectrum of ethylene (Price and Tutte, *loc. cit.*). Not only are

FIG. 2.

The figure indicates the dimensions of the excited orbitals of the 3200-, 2100-, 1830-, and 1545-A. bands of keten.



the vibrational patterns similar, but the higher members have practically identical term values. The first member of the series is a very poor fit in the formula, but, because of its obvious resemblance to the first Rydberg transition of ethylene, there is little doubt of its classification.

The short vibrational progressions associated with the members of series (1) show that the bands refer to excitation of an electron from a weakly-bonding orbital. The orbital concerned is undoubtedly of a π-type and, just as with ethylene, the series may be interpreted as $\pi \longrightarrow ns$. Since the bands of series (1) represent excitation of an electron from an orbital compounded from atomic L-shell orbitals, it is clearly better to make the upper orbital of the first member of the series have the principal quantum number 3 rather than 2. For this reason, the quantum defect of series (1) has been written as 1·07 instead of 0·07. The corresponding quantum defect for ethylene is 1·09.

The reason for the poor agreement of $\nu_{obs.}$ and $\nu_{calc.}$ for the first member of series (1) is obviously that the size of the upper orbital for that member is not sufficiently large for the nuclear framework to be regarded, in comparison, as a single atom. In order that the effects of the molecular dimensions on the excited orbital may be readily understood it is valuable to calculate approximate radii for the excited orbitals and to insert them on a scale diagram of the

molecule. These radii are calculated on the assumption that the term values of the states are inversely proportional to the effective radii ($V \propto 1/r$). The ionisation potential and combination radii of the electron in the ground state, together with the term value of the excited state, provide the necessary data. This has been done in Fig. 2 for the main bands of keten. The 3200-A. system of keten probably arises from the excitation of a non-bonding electron on the oxygen atom. If a radius of 0·6 A. and an ionization potential of *ca.* 11 v. for the 2pπ-oxygen electron are used, the effective radius of the excited state is calculated as 0·93 A. centred on the oxygen atom. Similarly for the band system around 2100 A., if this is interpreted as the transition of an electron from the C=O bonding orbital to an antibonding upper orbital ($\pi + \pi \longrightarrow \pi - \pi$). The excited orbital may be regarded, in an oversimplified way, as a circle of radius about 1·5 A. having its centre in the C=O bond. The upper orbitals of the 183 -, 1545,- 1493-, 1421-, and 1370-A. bands are indicated by circles centred on the C=C bond wit radii 2·2, 4·0, 4·9, 7·2, and 11·4 A. respectively. It can easily be seen that while the 3200- and the 2100-A. upper orbitals are within the molecular dimensions and must therefore be regarded as upper orbitals of intra-valence shell transitions, that of the 1830-A. band is just starting to clear the structure though it still occupies much space that might cause it to give rise to appreciable antibonding effects. These antibonding effects will tend to raise the height of the excited state above the value predicted by the Rydberg series and this is what is found ($\nu_{obs.} - \nu_{calc.} = 6641$ cm.$^{-1}$). The analogous band in ethylene at 1745 A. has an orbital of somewhat the same dimensions relative to its molecular structure (effective radius 2·1 A. centred on the double bond). It also deviates from the series formula by an amount that is comparable ($\nu_{obs.} - \nu_{calc.} = 2680$ cm.$^{-1}$), though somewhat smaller because of the less extended structure of ethylene relative to keten. The orbital of the 1545-A. band of keten is well clear of the molecular structure and can have but little effect on the binding of the molecule.

The slightly antibonding character of the first Rydberg orbitals relative to the higher ones is also brought out by the way the vibration frequencies change with the excitation. As the upper orbital of a member of series (1) changes from one comparable in size with the nuclear framework (the 1830-A. transition) to one large in comparison with it (the 1545-A. transition), the main frequencies of the vibrational pattern characteristic of the members rise from *ca.* 300 and *ca.* 860 cm.$^{-1}$ to *ca.* 620 and *ca.* 1025 cm.$^{-1}$. The 1630—1550-A. system (effective radius = 3·2 A.), although not a member of series (1),* shows intermediate frequency values. In the transitions at wave-lengths shorter than 1545 A., the vibrational frequencies remain roughly constant. In other words, (*a*) the transitions at 1545 A. and to shorter wave-lengths all have upper orbitals so extended that the excited electron has practically no effect on the binding between the atoms of the keten molecule, and (*b*) the 1830-A. transitions are to upper orbitals which possess some small anti-bonding character. (*b*) is further supported by the observed degradation to the red of bands in the 1830-A. system.

Just as for keten, the second member of the main Rydberg series found for ethylene has a long spacing greater than that of the first member; and subsequent members show spacings practically identical with those of the second member. The increase of the short spacing in keten from *ca.* 300 cm.$^{-1}$ to *ca.* 620 cm.$^{-1}$ shows that the interpretation of this spacing as representing a single quantum of the 529- or the 588-cm.$^{-1}$ ground-state vibrations is unlikely, but is compatible with the interpretation of the spacing as representing two quanta of such a vibration, as required by the selection rule.

In the spectrum of ethylene the first member (at 1745 A.) of the strongest Rydberg series is superimposed on a weaker region of continuous absorption reaching a maximum at 1630 A. A similar situation occurs for keten, the maximum of the continuous absorption being at 1700 A. The shift is about what is expected in view of the shifts of corresponding Rydberg series members in this wave-length region (Table VI). In ethylene it has been suggested that this transition is to be labelled $N \rightarrow V$ in the terminology of Mulliken (*J. Chem. Physics*, 1939, **7**, 14, 20) (cf. Walsh, *Ann. Reports*, 1947, **44**, 32).

Although the keten series (1) corresponds to the main Rydberg series of ethylene, its members are shifted considerably to long wave-lengths relative to the corresponding ethylene bands. The shifts are given in Table VI. As the upper orbital decreases in dimensions from the $n = 7$ to the $n = 6$ to the $n = 5$ member, the shift from ethylene to keten remains approximately constant. Actually it decreases slightly. From the $n = 5$ to the $n = 4$ member it decreases more rapidly and from the $n = 4$ to the $n = 3$ member it decreases most markedly. This is connected with the change of nature of the upper orbital from extra- to intra-valence shell type.

* It probably inaugurates a weaker Rydberg series analogous to one of the weaker series found for ethylene. The 1493-A. transition may be the second member.

It indicates that the main influence causing the ionisation potential of keten to be so much less than that of ethylene only comes into play when a π-electron is excited to an orbital large compared with the dimensions of the molecule. In other words it is a particular stability of $(CH_2{:}CO)^+$ rather than an instability of $CH_2{:}CO$ that causes the low ionisation potential. Stability of $(CH_2{:}CO)^+$ is probably due to the tendency of the 2pπ-O electrons to occupy the place vacated by the electron removed from the C:C bond : *i.e.*, delocalisation appears to be a much more important phenomenon in the higher excited states of $CH_2{:}CO$ and in $(CH_2{:}CO)^+$ than in the lower states. It is relevant here to point our that, in spite of the marked shift of the ionisation potential from ethylene to keten, (*a*) the force constants controlling stretching of the C:C bonds in ethylene and keten have been reported as identical (Linnett, *Quart. Reviews*, 1947, **1**, 85), (*b*) the C:C lengths in the two molecules are the same as determined by spectroscopic measurements (see Allen and Sutton, *Acta Crystall.*, 1950, **3**, 46) and (*c*) Kistiakowsky and Rosenberg find the rates of reaction of CH_2 with C_2H_4 and with $CH_2{:}CO$ to be almost identical (*J. Amer. Chem. Soc.*, 1950, **72**, 321) although the activation energy for reaction of a free radical or acceptor body with a π-electron system is usually less the lower the π^{-1} ionisation potential (see, *e.g.*, Chamberlain and Walsh, *Trans. Faraday Soc.*, 1949, **45**, 1032). There are therefore indications that, as regards the ground states, the C:C-π-orbital is not far from being equally tightly bound in keten and in ethylene. If so, delocalisation in the ground state of keten is probably small. Presumably it occurs to a limited extent but is largely balanced in its effect on the C:C orbital, by the inductive effect of the O atom, and the " acetylenic " nature of the central C atom in keten (Walsh, *J. Amer. Chem. Soc.*, 1946, **68**, 2408).

The electron impact value for the first ionisation potential of allene is at 9·9 v. (Delfosse and Bleakney, *Physical Rev.*, 1940, **58**, 787), and thus lies between the values for keten and ethylene (10·50 and 9·60 v., respectively). The big decrease from ethylene to keten we have explained as probably due to conjugation between the C-C-π- and the O-2pπ-electrons in the $(CH_2{:}CO)^+$ ion. The smaller decrease from ethylene to allene is then easily explicable as caused by the reduced conjugating power of a CH_2 group relative to that of an O atom. Similar stabilisation effects in ionic states have been suggested by Price (*Chem. Rev.*, 1947, **41**, 257) to be the most frequent cause of the reduction of the ionisation potentials of particular electron groups in molecules.

Judging from the spectra of aldehydes and ketones the Rydberg bands of the 2pπ-O-electrons of keten should have appeared in the region below 1700 A. Failure to detect these calls for an explanation. It is suggested that the ionisation potential of these electrons is considerably greater in keten than, for example, in acetaldehyde where the value is 10·23 v. (Walsh, *Trans. Faraday Soc.*, 1945, **41**, 498). This indeed is to be expected from the reduced polarity of the CO bond of keten relative to that of acetaldehyde (Walsh, *J. Amer. Chem. Soc.*, 1946, **68**, 2408). This reduced polarity can be regarded theoretically as due to the digonal nature of the central carbon atom in keten and is supported by experimental evidence from a variety of sources (Walsh, *ibid.*, p. 2408). It has also to be remembered that any conjugation that occurs between the π-C:C-electrons and the 2pπ-O-electrons (the former corresponding to the lower ionisation potential) will push the C:C levels up and the O levels down. Similar effects occur in vinyl chloride (Price and Tutte, *loc. cit.*; Walsh, *Trans. Faraday Soc.*, 1945, **41**, 35), and in monochlorobenzene (Price and Walsh, *Proc. Roy. Soc.*, 1947, *A*, **191**, 22). On the other hand, the ionisation potential of the 2pπ-O-electrons in keten should be lower than that in carbon dioxide (13·79 v.) in view of the lowered electronegativity of a CH_2 group relative to an oxygen atom. If the value turns out to be about 12 v., then the Rydberg bands would fall considerably to the short wave-lengths of the C:C double-bond Rydberg bands. In fact they are probably obscured by bands which appeared on our plates but which were due to water present as an impurity. That the lowest ionisation potential of the keten molecule should be that of the π-orbital of the C:C bond helps to explain the reaction of methylene with the keten molecule. The reaction may be pictured (Walsh, *J.*, 1947, 89) as

$$CH_2 + CH_2{=}C{=}O \longrightarrow CH_2{=}C{=}O \longrightarrow C_2H_4 + CO$$
$$\downarrow$$
$$CH_2$$

There seems to be no special difficulty arising from the high CO ionisation potential in the explanation of the long-wave shift of the near ultra-violet bands of keten (~3200 A.). The relatively positive character of the CO group will increase the binding of both the ground and the low excited state, and the latter will be still further stabilised by the tendency of the C:C-π-

electrons to occupy the place in the 2pπ-O orbital vacated by the excited electrons, *i.e.*, for the C:C orbital to become more delocalised in the excited state. The long-wave-length shift can thus be accounted for.

One of us (W. C. P.) acknowledges assistance by the U.S. Office of Naval Research under Task Order IX of Contract N6—ori 20 with the University of Chicago. Another (J. P. T.) thanks the Commissioners for the Exhibition of 1851 for the award of an Overseas Scholarship (for Eire), during the tenure of which this work was carried out. We are also grateful to the Royal Society and to the Chemical Society for grants for equipment, and to Professor C. A. Coulson for discussion in connection with this paper.

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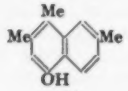
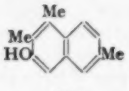
207. *The Action of Methylsuccinic Anhydride on Certain Xylenols, and Synthesis of Some Trimethylnaphthols.*

By WESLEY COCKER, A. K. FATEEN, and CYRIL LIPMAN.

The condensation of methylsuccinic anhydride with *o*-3-, *o*-4-, *m*-4-, and *p*-xylenol has been investigated. 3 : 4 : 6-Trimethyl-1-, 3 : 4 : 7-trimethyl-2-, 2 : 4 : 7-trimethyl-1-, and 1 : 4 : 7-trimethyl-2-naphthols (I to IV, respectively) have been prepared.

THE condensation of unsymmetrical succinic anhydrides with aromatic compounds has been extensively studied (cf. Berliner, *Org. Reactions*, 1949, **5**, 242, 275; Bhatt and Nargund, *J. Univ. Bombay*, 1942, II, 131; Cocker *et al.*, *J.*, 1950, 1781; *Chem. and Ind.*, 1949, 641, who review earlier work in this field). It has been shown that, in general, in ionising solvents, α-alkyl(or aryl)-β-aroylpropionic acids are the main products, but in non-ionising solvents the formation of β-alkyl(or aryl)-β-aroylpropionic acids is favoured. We have condensed the methyl ethers


(I.)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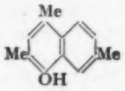
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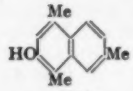

(IV.)

of the above xylenols with methylsuccinic anhydride in nitrobenzene, in benzene, and in carbon disulphide. The results of these reactions are expressed in the following table, the relative proportions of products being only approximate.

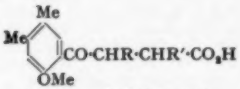
Methyl xylyl ether.	Solvent.	Products : -α- or -β-methylpropionic acid.	α-Isomer, parts.	β-Isomer, parts.
o-4-Xylyl	(*a*) $C_6H_5{\cdot}NO_2$	β-(2-Methoxy-4 : 5-dimethylbenzoyl)-	10	1
	(*b*) C_6H_6 (hot)	β-(2-Hydroxy-4 : 5-dimethylbenzoyl)-	3	1
	,, (cold)	β-Benzoyl-	—	None
o-3-Xylyl	(*a*) $C_6H_5{\cdot}NO_2$ (cold)	β-(4-Methoxy-2 : 3-dimethylbenzoyl)-	8	1
	(*b*) C_6H_6 (cold)	,, ,, ,,	2	1
m-4-Xylyl	(*a*) $C_6H_5{\cdot}NO_2$	β-(5-Methoxy-2 : 4-dimethylbenzoyl)-	—	None
	(*b*) C_6H_6 (cold or hot)	β-Benzoyl-	—	None
	(*c*) CS_2 (cold)	(No reaction)		
p-Xylyl	(*a*) $C_6H_5{\cdot}NO_2$	β-(4-Methoxy-2 : 5-dimethylbenzoyl)-	—	None
	(*b*) C_6H_6 (hot)	β-Benzoyl-	—	None
	(*c*) CS_2 (cold)	(No reaction)		
	,, (hot)	α-Isomer		

In general, the results conform with previous experience, although it is noteworthy that in the attempted condensation of methylsuccinic anhydride with three of the xylyl ethers in benzene, reaction took place with the solvent in preference to the ether.

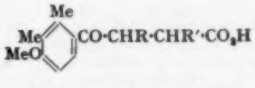
Each keto-acid was reduced to the corresponding butyric acid, which was cyclised to the tetralone, from which the required naphthol was obtained by conventional methods. The identity of the keto-acids was determined (*a*) by oxidation with sodium hypochlorite to the

known corresponding methoxydimethylbenzoic acid and (*b*) by attempted formation of a semicarbazone of the tetralone obtained, as described above, from the keto-acid. As mentioned by Cocker *et al.* (*J.*, 1950, 1781; cf. Cagniant and Buu-Hoï, *Bull. Soc. chim.*, 1942, **9**, 841), failure of a 1-tetralone to yield a semicarbazone suggests the presence of groups at the 2- and the 8-position. Those semicarbazones which could be formed are described.

The light-absorption characteristics (see Experimental) of the pairs of 1- and 2-naphthols are in agreement with those already described by Cocker *et al.* (*loc. cit.*). Again, the 1- may be clearly distinguished from the 2-naphthols.



(V; R = H, R′ = Me.)
(VI; R = Me, R′ = H.)



(VII; R = H, R′ = Me.)
(VIII; R = Me, R′ = H.)

Experimental.

(Analyses are by Drs. Weiler and Strauss, Oxford.)

Absorption spectra were measured with a Beckman Quartz Spectrophotometer, Model D.U., silica cells of thickness 1·000 ± 0·001 cm. being used. Spectra were measured in alcohol, and the initial concentrations were of the order of 20 mg./l., with ten-fold dilution when necessary to bring the high-intensity peaks within the range of the instrument.

A. *Experiments with* o-4-*Xylenol.*

3 : 4 : 6-*Trimethyl*-1-*naphthol* (I).—**β-(2-*Methoxy*-4 : 5-*dimethylbenzoyl*)-α- *and* -β-*methylpropionic acids*** (**V** *and* **VI**). A mixture of methyl *o*-4-xylyl ether (10 g.), methylsuccinic anhydride (10 g.), and dry nitrobenzene (25 c.c.) was slowly treated with a solution of aluminium chloride (25 g.) in nitrobenzene (75 c.c.) at 15—20°, and the mixture was set aside overnight. It was poured into ice and hydrochloric acid, and the solid product (13 g.), consisting largely of (V), m. p. 162—168°, was collected. After being washed with water it was recrystallised from dilute alcohol, yielding needles (10 g.), m. p. 167—168° (Found: C, 67·5; H, 7·3. Calc. for $C_{18}H_{18}O_4$: C, 67·2; H, 7·2%) (Ruzicka *et al.*, *Helv. Chim. Acta*, 1936, **19**, 370, who prepared this ketone by another route, described it as a liquid). Its *semicarbazone* crystallised from dilute alcohol as needles, m. p. 179—180° (Found: C, 58·9; H, 7·1. $C_{19}H_{21}O_4N_3$ requires C, 58·6; H, 6·8%). The nitrobenzene layer from the above condensation was separated, washed successively with hydrochloric acid and water, and extracted several times with 20% ammonia solution. The extract was washed with ether, filtered, and acidified, yielding the *keto-acid* (VI) (1 g.), m. p. 78—88°, which crystallised from benzene–light petroleum (b. p. 40—60°) as needles, m. p. 110° (Found: C, 67·1; H, 7·2. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%). Its *semicarbazone* crystallised from ethyl acetate as needles, m. p. 168—169° (Found: C, 58·6; H, 7·0. $C_{15}H_{21}O_4N_3$ requires C, 58·6; H, 6·8%).

β-(2-*Hydroxy*-4 : 5-*dimethylbenzoyl*)-α- *and* -β-*methylpropionic acids*. A mixture of methyl *o*-4-xylyl ether (4 g.), methylsuccinic anhydride (4 g.), and dry benzene (70 c.c.) was slowly treated with aluminium chloride (10 g.), then refluxed for 2 hours and set aside overnight. It was poured into ice and hydrochloric acid, and the benzene layer separated. After being washed with water, the benzene was removed under reduced pressure and the solid residue was purified by solution in sodium carbonate and reprecipitation. The mixture of keto-acids (6·2 g.; m. p. 125—140°) on repeated crystallisation, alternately from benzene and dilute alcohol, gave a *keto-acid* (3·4 g.), m. p. 158° (Found: C, 66·1; H, 7·2. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%), identical with the product of demethylation of β-(2-methoxy-4 : 5-dimethylbenzoyl)-α-methylpropionic acid (V) with hydriodic acid. From the mother-liquors of the above crystallisations a second keto-acid (1·3 g.), m. p. 142°, identical with the product of demethylation of β-(2-methoxy-4 : 5-dimethylbenzoyl)-β-methylpropionic acid (VI) was obtained.

γ-(2-*Methoxy*-4 : 5-*dimethylphenyl*)-α-*methylbutyric acid*. The keto-acid (V) (9 g.) was refluxed for 48 hours with amalgamated zinc (100 g.), concentrated hydrochloric acid (120 c.c.), and water (90 c.c.) and yielded the required acid (7 g.), b. p. 212°/17 mm. (cf. Ruzicka *et al.*, *loc. cit.*).

5 : 6 : 7 : 8-*Tetrahydro*-5-*keto*-3 : 4 : 6-*trimethyl*-1-*naphthol*, obtained when the butyric acid (3·5 g.) was heated on the water-bath for 2 hours with 80% sulphuric acid, crystallised from dilute alcohol as needles (0·7 g.), m. p. 108—109° (Found: C, 76·2; H, 7·9. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%). Its methyl ether was obtained when the butyric acid (1 g.) was heated on the water-bath for 10 minutes with 98% sulphuric acid (5 g.). It crystallised from dilute alcohol as needles (0·7 g.), m. p. 56° (cf. Ruzicka *et al.*, *loc. cit.*, who describe this as a liquid) (Found: C, 77·0; H, 7·9. Calc. for $C_{14}H_{18}O_2$: C, 77·1; H, 8·3%).

5 : 6 : 7 : 8-*Tetrahydro*-3 : 4 : 6-*trimethyl*-1-*naphthol*. The above hydroxy-ketone (1·1 g.) was reduced during 24 hours with a mixture of concentrated hydrochloric acid (70 c.c.), water (50 c.c.), amalgamated zinc (30 g.), and benzene (20 c.c.). From the benzene layer the *hydroxy-tetralin* (0·7 g.) was obtained as small needles (from dilute alcohol), m. p. 120° (Found: C, 82·1; H, 9·2. $C_{13}H_{18}O$ requires C, 82·1; H, 9·5%). Its *methyl ether* was obtained in a similar manner from the methoxy-tetralone (0·6 g.) as colourless plates (0·5 g.) m. p. 50° (Found: C, 82·6; H, 9·7. $C_{14}H_{20}O$ requires C, 82·4; H, 9·8%).

3 : 4 : 6-*Trimethyl*-1-*naphthol* (I). The hydroxy-tetralin (0·7 g.) was heated with selenium (2·1 g.) for 2·5 hours at 335—340°, and the product extracted with methanol (charcoal) and distilled in steam. The distillate yielded the *naphthol* (0·1 g.), which crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 99—100° (Found : C, 83·7; H, 7·5. $C_{13}H_{14}O$ requires C, 83·9; H, 7·5%). Light absorption : Maxima, 2420, 3070 (3200), and 3300 A.; log ε = 4·65, 3·70 (3·65), and 3·57, respectively. Its *picrate* separated from benzene as scarlet needles, m. p. 159—160° (Found : C, 54·8; H, 4·4. $C_{19}H_{17}O_8N_3$ requires C, 54·9; H, 4·1%). Its methyl ether formed needles (from alcohol), m. p. 88° (cf. Ruzicka *et al.*, *loc. cit.*) (Found : C, 85·0; H, 8·3. Calc. for $C_{14}H_{16}O$: C, 84·0; H, 8·0%).

B. *Experiments with* o-3-*Xylenol.*

3 : 4 : 7-*Trimethyl*-2-*naphthol* (II).—**β-(4-*Methoxy*-2 : 3-*dimethylbenzoyl*)-α-*methyl-* and *-β-methyl-propionic acids*** (VII *and* VIII). Methyl *o*-3-xylyl ether (8 g.), methylsuccinic anhydride (8 g.), and aluminium chloride (21 g.) in nitrobenzene (50 c.c.) were allowed to react. The mixture was decomposed with ice and hydrochloric acid, and the solid *acid* (VII) (10 g.) was collected, and crystallised from benzene–light petroleum as plates (8·5 g.), m. p. 137° (Found : C, 67·3; H, 7·2. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%). Its *semicarbazone* crystallised from dilute alcohol as needles, m. p. 196° (Found : C, 59·2; H, 7·0. $C_{15}H_{21}O_4N_3$ requires C, 58·6; H, 6·8%). The residual nitrobenzene from the above was extracted with aqueous ammonia, and the extract shaken with ether and acidified with hydrochloric acid, giving impure **β-(4-*methoxy*-2 : 3-*dimethylbenzoyl*)-β-*methylpropionic acid*** (VIII) (3·5 g.), m. p. 111—115°, which crystallised from benzene as plates (1·2 g.), m. p. 112—113° (Found : C, 67·5; H, 7·4. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%).

γ-(4-Methoxy-2 : 3-dimethylphenyl)-α-methylbutyric acid, prepared by reduction of the keto-acid (VII) (8·5 g.), crystallised from benzene–light petroleum as needles (6·5 g.), m. p. 98—99°.

5 : 6 : 7 : 8-*Tetrahydro*-8-*keto*-3 : 4 : 7-*trimethyl*-2-*naphthol* was obtained when the preceding acid (3·5 g.) was heated for 2 hours on the water-bath with 80% sulphuric acid. It crystallised from benzene as needles (1 g.), m. p. 204° (Found : C, 76·3; H, 7·8. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%). Its *methyl ether* crystallised from dilute alcohol as plates, m. p. 76—77° (Found : C, 77·8; H, 7·8. $C_{14}H_{18}O_2$ requires C, 77·1; H, 8·3%). The *semicarbazone* of the methyl ether crystallised from dilute alcohol as plates, m. p. 217—218° (Found : C, 65·6; H, 7·7. $C_{15}H_{21}O_2N_3$ requires C, 65·5; H, 7·6%). **5 : 6 : 7 : 8-*Tetrahydro*-3 : 4 : 7-*trimethyl*-2-*naphthol*** was obtained when the hydroxy-tetralone (0·5 g.) was reduced in benzene under Clemmensen conditions. It separated from light petroleum (b. p. 40—60°) as long needles (0·2 g.), m. p. 104—105° (Found : C, 81·4; H, 9·3. $C_{13}H_{18}O$ requires C, 82·1; H, 9·5%).

3 : 4 : 7-*Trimethyl*-2-*naphthol* (II). The preceding compound (0·6 g.) was dehydrogenated with selenium (1·8 g.) at 340—360° for 3 hours. The *naphthol* (0·2 g.) separated from light petroleum (b. p. 60—80°) as long shining needles, m. p. 141° (Found : C, 83·5; H, 7·9. $C_{13}H_{14}O$ requires C, 83·9; H, 7·5%). Light absorption : Maxima, 2340 (2770), 2860 (2970), 3180, and 3320 A.; log ε = 4·9 (3·66), 3·73 (3·60), 3·29, and 3·40, respectively. Its *picrate* crystallised from benzene as scarlet needles, m. p. 152—153° (Found : C, 55·7; H, 3·9. $C_{19}H_{17}O_8N_3$ requires C, 54·9; H, 4·1%). Its *trinitrobenzene* adduct crystallised from benzene as orange needles, m. p. 164° (Found : C, 57·0; H, 4·3. $C_{19}H_{17}O_7N_3$ requires C, 57·1; H, 4·3%).

γ-(4-Methoxy-2 : 3-dimethylphenyl)-β-methylbutyric acid, prepared from the keto-acid (VIII) (1·3 g.) by reduction with amalgamated zinc, separated (1·2 g.) from light petroleum (b. p. 60—80°) as needles, m. p. 115° (Ruzicka *et al.*, *loc. cit.*, who prepared this acid by another route, give m. p. 107—108°) (Found : C, 70·9; H, 8·1. Calc. for $C_{14}H_{20}O_3$: C, 71·2; H, 8·4%). **5 : 6 : 7 : 8-*Tetrahydro*-8-*keto*-3 : 4 : 6-*trimethyl*-2-*naphthol*** was obtained from the preceding butyric acid (1·1 g.) on cyclisation with 80% sulphuric acid. It separated from alcohol as needles (0·4 g.), m. p. 128—129° (Found : C, 77·0; H, 8·2. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%). **5 : 6 : 7 : 8-*Tetrahydro*-3 : 4 : 6-*trimethyl*-2-*naphthol***, obtained from this tetralone (0·3 g.) in the usual manner, separated from alcohol as needles (0·1 g.), m. p. 61—62° (Found : C, 81·9; H, 10·1. $C_{13}H_{18}O$ requires C, 82·1; H, 9·5%).

C. *Experiments with* m-4-*Xylenol.*

2 : 4 : 7-*Trimethyl*-1-*naphthol* (III).—**β-(5-*Methoxy*-2 : 4-*dimethylbenzoyl*)-α-*methylpropionic acid*** was obtained in the usual way from methyl *m*-4-xylyl ether (12 g.) in nitrobenzene. The crude product (17 g.) was recrystallised from dilute alcohol, from which the required acid separated as plates, m. p. 110° (Found : C, 67·3; H, 7·3. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%). Its *semicarbazone* crystallised from dilute alcohol as needles, m. p. 169° (Found : C, 58·2; H, 6·9. $C_{15}H_{21}O_4N_3$ requires C, 58·6; H, 6·8%). γ-(5-Methoxy-2 : 4-dimethylphenyl)-α-methylbutyric acid, prepared from the acid (7 g.), distilled at 180°/20 mm. (6·5 g.).

5 : 6 : 7 : 8-*Tetrahydro*-8-*keto*-2 : 4 : 7-*trimethyl*-1-*naphthol*. The above compound (6 g.) was heated with 80% sulphuric acid (24 g.) for 2 hours. The ***keto-naphthol*** separated from dilute alcohol as pale yellow prisms (3 g.), m. p. 56—57° (Found : C, 76·0; H, 7·6. $C_{13}H_{14}O_2$ requires C, 76·5; H, 7·8%).

5 : 6 : 7 : 8-*Tetrahydro*-2 : 4 : 7-*trimethyl*-1-*naphthol* crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 71—72° (Found : C, 81·6; H, 9·3. $C_{13}H_{18}O$ requires C, 82·1; H, 9·5%).

2 : 4 : 7-*Trimethyl*-1-*naphthol* (III). The preceding compound (0·7 g.) was heated with selenium (3·1 g.) at 340—360° for 3 hours. The product was sublimed and then crystallised from light petroleum (b. p. 40—60°), from which the required *naphthol* separated as long needles, m. p. 105—106° (Found : C, 83·7; H, 7·6. $C_{13}H_{14}O$ requires C, 83·9; H, 7·5%). Light absorption : Maxima, 2420, 3030 (3160), and 3300 A.; log ε = 4·63, 3·69 (3·62), and 3·47, respectively. Its *picrate* crystallised from benzene as scarlet needles, m. p. 138—139° (Found : C, 54·6; H, 4·3. $C_{19}H_{17}O_8N_3$ requires C, 54·9; H, 4·1%). Its *carbanilate* crystallised from alcohol as small needles, m. p. 166—167° (Found : C, 78·5; H, 6·2. $C_{20}H_{19}O_2N$ requires C, 78·7; H, 6·2%).

D. *Experiments with* p-*Xylenol.*

1 : 4 : 7-*Trimethyl*-2-*naphthol* (IV).—β-(4-*Methoxy*-2 : 5-*dimethylbenzoyl*)-α-*methylpropionic acid.* Methyl *p*-xylyl ether (8·5 g.) was condensed with methylsuccinic anhydride (8·5 g.) by use of aluminium chloride (22 g.) in nitrobenzene (70 c.c.). The crude product (5 g.), m. p. 136—139°, when crystallised from dilute alcohol yielded the required *acid* as plates, m. p. 140° (Found : C, 67·0; H, 7·2. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%). Its *semicarbazone* separated from dilute alcohol as needles, m. p. 166° (Found : C, 58·6; H, 7·0. $C_{15}H_{21}O_4N_3$ requires C, 58·6; H, 6·8%).

γ-(4-*Methoxy*-2 : 5-*dimethylphenyl*)-α-*methylbutyric acid.* The keto-acid (4 g.) was reduced by amalgamated zinc (50 g.) to the required *butyric acid*, which separated from light petroleum (b. p. 40—60°) as large prisms (3·2 g.), m. p. 89—90° (Found : C, 70·9; H, 7·7. $C_{14}H_{20}O_3$ requires C, 71·2; H, 8·4%).

5 : 6 : 7 : 8-*Tetrahydro*-8-*keto*-1 : 4 : 7-*trimethyl*-2-*naphthol.* The above acid (2·5 g.) was heated with 80% sulphuric acid (10 g.) on the water-bath for 2 hours and yielded the required *tetralone*, which crystallised from light petroleum (b. p. 40—60°) as prisms, m. p. 75° (Found : C, 76·5; H, 7·7. $C_{13}H_{16}O_2$ requires C, 76·5; H, 7·8%).

5 : 6 : 7 : 8-*Tetrahydro*-1 : 4 : 7-*trimethyl*-2-*naphthol.* The foregoing ketone (1·1 g.) was reduced with amalgamated zinc and hydrochloric acid. The required *hydroxy-tetralin* separated from light petroleum (b. p. 40—60°) as needles, m. p. 32° (Found : C, 81·7; H, 9·5. $C_{13}H_{18}O$ requires C, 82·1; H, 9·5%).

1 : 4 : 7-*Trimethyl*-2-*naphthol* (IV). The hydroxy-tetralin (0·2 g.) was heated with selenium (0·6 g.) at 340—350° for 2 hours and yielded the required *naphthol*, which was extracted from the mixture with methyl alcohol and crystallised from dilute alcohol, from which it separated as long needles, m. p. 48—49° (Found : C, 83·9; H, 7·7. $C_{13}H_{14}O$ requires C, 83·9; H, 7·5%). Light absorption : Maxima, 2370, 2880 (3020), 3250, and 3370 A.; log ε = 4·59, 3·56 (3·46), 3·09, and 3·13, respectively. Its picrate crystallised from benzene as scarlet needles, m. p. 115°, but there was insufficient (2·3 mg.) for analysis.

The authors thank Mr. E. R. Stuart for the light-absorption measurements, Imperial Chemical Industries Limited, Billingham Division, for gifts of xylenols, the Medical Research Council of Ireland for a grant, and the Egyptian Government for a grant (A. K. F.).

TRINITY COLLEGE, DUBLIN. [*Received, December 1st*, 1950.]

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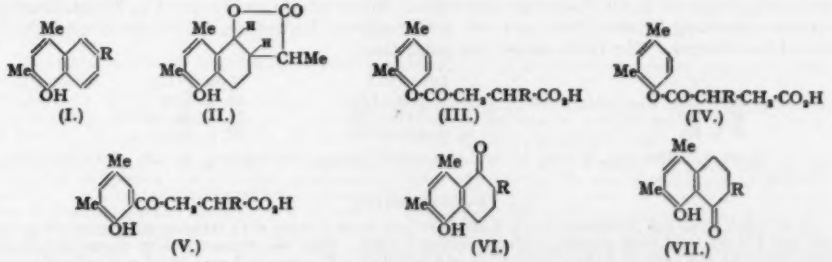
208. *The Constitution of ψ-Santonin. Part VIII. Synthesis of 6-Ethyl-2 : 4-dimethyl-1-naphthol.*

By WESLEY COCKER, A. K. FATEEN, and CYRIL LIPMAN.

6-Ethyl-2 : 4-dimethyl-1-naphthol (I; R = Et) and 2 : 4 : 6-trimethyl-1-naphthol (I; R = Me) have been synthesised. The former is identical with the product of dehydrogenation of desmotropo-ψ-santonin (Cocker *et al.*, *J.*, 1950, 1781).

COCKER *et al.* (*loc. cit.*) dehydrogenated desmotropo-ψ-santonin with palladised charcoal and obtained a product which they concluded was 6-ethyl-2 : 4-dimethyl-1-naphthol (I; R = Et). Synthesis of this compound has shown the conclusion to be correct and there is now little doubt that (II) adequately represents the desmotropo-compound (cf. previous papers in this series).



(I.) (II.) (III.) (IV.) (V.) (VI.) (VII.)

Condensation of succinic anhydride and its derivatives with methyl *m*-4-xylyl ether in presence of aluminium chloride takes place predominantly *meta* to the methoxy-group. Alkylsuccinic anhydrides yield largely α-alkyl-β-(5-hydroxy-2 : 4-dimethylbenzoyl)propionic acids, the corresponding β-alkyl compounds being produced in negligible yield (cf. Cocker, Lipman, and Whyte, *J.*, 1950, 1519; Cocker *et al.*, *loc. cit.*; Cocker, Fateen, and Lipman, preceding

paper). Thus, workable yields of the tetralones of type (VI; R = alkyl) cannot be obtained by this means. However, rearrangement of the alkylsuccinic esters of *m*-4-xylenol (cf. Cocker, *J.*, 1946, 36) could possibly yield keto-acids of type (V; R = alkyl) which would form the starting points for the synthesis of the tetralones mentioned and, hence, of 6-alkyl-2 : 4-dimethyl-1-naphthols.

In model experiments, *m*-4-xylenol was esterified with succinic anhydride and the ester (III or IV; R = H) was rearranged with aluminium chloride to β-(2-hydroxy-3 : 5-dimethyl benzoyl)propionic acid. Attempts to oxidise this acid to the corresponding benzoic acid failed, but there can be little doubt as to its structure in view of the fact that (*a*) it differs from β-(5-hydroxy-2 : 4-dimethylbenzoyl)propionic acid obtained by demethylation of its methyl ether (Cocker and Lipman, *J.*, 1947, 533; Cocker, Lipman, and Whyte, *loc. cit.*), and (*b*) the corresponding butyric acid readily cyclised to 5 : 6 : 7 : 8-tetrahydro-5-keto-2 : 4-dimethyl-1-naphthol (VI; R = H) which differs from the tetralone (VII; R = H) obtained by the workers mentioned, but (*c*) it yields the same tetralin as was obtained by these workers.

m-4-Xylenol, esterified with ethylsuccinic anhydride, gave a mixture of esters (III and IV; R = Et) from which a pure ester was isolated. Its exact nature is being investigated. The ester was rearranged with aluminium chloride, and a pure keto-acid was obtained. Attempts to oxidise this acid failed, but (*a*) it differed from α-ethyl-β-(5-hydroxy-2 : 4-dimethylbenzoyl)-propionic acid (Cocker *et al.*, *loc. cit.*), and (*b*) it could not be methylated. The latter experience is reminiscent of our attempts to methylate the " hindered " hydroxyl group of 2-hydroxy-3 : 5-dimethylbenzoic acid, whilst the isomer 5-hydroxy-2 : 4-dimethylbenzoic acid can be readily methylated. There seems to be no doubt, therefore, that *ortho*-migration takes place in the Fries reaction. The keto-acid, first reduced to the butyric acid, gave a tetralone, different from (VII; R = Et), which did not yield a semicarbazone and must, therefore, possess a hindered carbonyl group (cf. Cagniant and Buu-Hoï, *Bull. Soc. chim.*, 1942, **9**, 841; Cocker *et al.*, *loc. cit.*). In view of this evidence, the keto-acid must be represented as (V; R = Et) and the tetralone as (VI; R = Et). Reduction of the tetralone and dehydrogenation of the product yielded 6-ethyl-2 : 4-dimethyl-1-naphthol (I), which along with its picrate and trinitrobenzene adduct was identical with the " natural " naphthol of Cocker *et al.* (*loc. cit.*) and its corresponding derivatives, and differed from 7-ethyl-2 : 4-dimethyl-1-naphthol (Cocker *et al.*, *loc. cit.*).

Two pure esters, m. p.s 112—113° and 65°, respectively, were isolated from the reaction between *m*-4-xylenol and methylsuccinic anhydride. The former ester was rearranged and yielded the keto-acid (V; R = Me), which gave the hydroxy-tetralone (VI; R = Me). This gave no semicarbazone and differed from the isomer (VII; R = Me) described by Cocker, Fateen, and Lipman (preceding paper). 2 : 4 : 6-Trimethyl-1-naphthol was obtained from the tetralone by conventional methods and characterised as its picrate and trinitrobenzene adduct.

The second ester, m. p. 65°, was also rearranged to a keto-acid, but this was obtained in such small yields that little could be done to establish its constitution. It is possibly β-(2-hydroxy-3 : 5-dimethylbenzoyl)-β-methylpropionic acid.

The melting points of the isomeric hydroxy-tetralones (types VI and VII) are interesting and provide further evidence for the structures of the tetralones (type VI) obtained through the keto-acids produced in the Fries rearrangement. In the tetralones of type (VI), intramolecular hydrogen bonding between hydroxyl and keto-groups is impossible, but those of type (VII) should be chelated. The table makes this point clear.

	Type (VI).	Type (VII).
R = H	M. p. 180—181°	M. p. 61·5° [1]
R = Me	M. p. 147—148°	M. p. 56—57° [2]
R = Et	M. p. 105—106°	M. p. 28° [2]

[1] Cocker, Lipman, and Whyte, *loc. cit.* [2] Cocker, Fateen, and Lipman, *loc. cit.* [3] Cocker *et al.*, *loc. cit.*

Experimental.

m-4-*Xylyl Hydrogen Succinate.*—*m*-4-Xylenol (5 g.), when heated with succinic anhydride (5 g.) at 130° for 3 hours and then rapidly chilled, yielded a solid. This was extracted with aqueous sodium carbonate, and the extract washed with ether and acidified. The required *ester* (8 g.) was collected and dried. It crystallised from benzene–light petroleum as colourless rods (6·8 g.), m. p. 78° (Found: C, 64·7; H, 6·7. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%).

β-(2-*Hydroxy*-3 : 5-*dimethylbenzoyl*)*propionic Acid.*—A solution of the above ester (2 g.) in nitrobenzene (30 c.c.) was heated to 140°, and aluminium chloride (8 g.) in nitrobenzene (100 c.c.) was added. The mixture was heated for 0·5 hour, cooled, and decomposed with ice and hydrochloric acid. The product was purified by dissolution in aqueous sodium carbonate, filtration, acidification, and finally

crystallisation from dilute alcohol, from which the *keto-acid* (0·3 g.) separated as shining needles, m. p. 147—148° (Found : C, 64·9; H, 6·5. $C_{13}H_{16}O_4$ requires C, 64·9; H, 6·3%).

γ-(2-Hydroxy-3 : 5-dimethylphenyl)butyric Acid.—The keto-acid (1·1 g.), reduced with amalgamated zinc, yielded the required *acid* (0·3 g.) which separated from light petroleum as hair-like needles, m. p. 82° (Found : C, 69·2; H, 7·7. $C_{13}H_{18}O_3$ requires C, 69·2; H, 7·7%).

5 : 6 : 7 : 8-*Tetrahydro-5-keto-2 : 4-dimethyl-1-naphthol* (0·2 g.) was obtained from the preceding acid (0·3 g.) on treatment with concentrated sulphuric acid (1·5 g.). It crystallised from benzene–light petroleum as needles, m. p. 180—181° (Found : C, 75·7; H, 7·5. $C_{13}H_{14}O_2$ requires C, 75·8; H, 7·4%). Its *semicarbazone* crystallised from dilute alcohol as needles, m. p. 226—227° (Found : C, 63·9; H, 6·9. $C_{13}H_{17}O_2N_3$ requires C, 63·2; H, 6·9%).

β-(5-Hydroxy-2 : 4-dimethylbenzoyl)propionic acid obtained from its methyl ether (Cocker and Lipman, *J.*, 1947, 533; Cocker, Lipman, and Whyte, *J.*, 1950, 1519) consisted of plates, m. p. 139° (Found : C, 64·5; H, 6·8. $C_{12}H_{14}O_4$ requires C, 64·9; H, 6·3%).

2 : 4 : 6-*Trimethyl-1-naphthol* (I; R = Me).—m-4-*Xylyl esters of methylsuccinic acid.* A mixture of the xylenol (5 g.) and methylsuccinic anhydride (5 g.) was heated at 140° for 4 hours. After chilling, extraction with sodium carbonate solution, and reprecipitation, a solid (7·5 g.; m. p. 85—105°) was obtained. Crystallisation from benzene–light petroleum yielded two *esters*, A (2·6 g.; m. p. 112—113°) (Found : C, 66·1; H, 6·8. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%), and B (0·45 g.; m. p. 65°) (Found : C, 65·2; H, 6·6%).

Fries rearrangement of ester A. The ester (2 g.) was stirred and heated with aluminium chloride (6 g.) for 40 minutes at 140°, and was then decomposed in the usual way. The dark solution was extracted with ether from which a sticky solid (1·4 g.) was obtained. It was crystallised from benzene (charcoal) and obtained (0·9 g.) as needles, m. p. 122°. This was considered to be *β-(2-hydroxy-3 : 5-dimethylbenzoyl)-α-methylpropionic acid* (Found : C, 65·9; H, 6·8. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

5 : 6 : 7 : 8-*Tetrahydro-5-keto-2 : 4 : 6-trimethyl-1-naphthol* (0·2 g.) was obtained by reduction of the above keto-acid with amalgamated zinc, and cyclisation of the resultant liquid butyric acid (0·6 g.) with 98% sulphuric acid. It crystallised from benzene–light petroleum as needles, m. p. 148—149° (Found : C, 76·2; H, 7·7. $C_{13}H_{16}O_2$ requires C, 76·4; H, 7·8%). It did not form a semicarbazone.

5 : 6 : 7 : 8-*Tetrahydro-2 : 4 : 6-trimethyl-1-naphthol*, prepared by reduction of the hydroxytetralone (0·6 g.) with amalgamated zinc, crystallised from light petroleum as needles (0·5 g.), m. p. 91° (Found : C, 81·9; H, 9·7. $C_{13}H_{18}O$ requires C, 82·1; H, 9·5%).

2 : 4 : 6-*Trimethyl-1-naphthol* (I; R = Me). The above hydroxy-tetralin (0·4 g.) was heated with selenium (1·2 g.) for 2·5 hours at 340°. The *product* (0·15 g.) separated from light petroleum (b. p. 40—60°) as needles, m. p. 123° (Found : C, 83·6; H, 7·6. $C_{13}H_{14}O$ requires C, 83·9; H, 7·5%). Light absorption : Max., 2410, 3030 (3180), and 3330 A.; log ε = 4·59, 3·66 (3·53), and 3·41 respectively. Its *picrate* crystallised from benzene as scarlet needles, m. p. 162° (Found : C, 55·3; H, 4·4. $C_{19}H_{17}O_8N_3$ requires C, 54·9; H, 4·1%). Its *trinitrobenzene* adduct crystallised from benzene as orange needles, m. p. 170° (Found : C, 56·9; H, 4·6. $C_{19}H_{17}O_7N_3$ requires C, 57·2; H, 4·3%).

Fries rearrangement of ester (B). The ester (1·7 g.) was treated as (A) and yielded a heavy oil which solidified and was crystallised several times from benzene–light petroleum from which the *keto-acid* separated as plates, m. p. 133° (Found : C, 65·3; H, 6·6. $C_{13}H_{16}O_4$ requires C, 66·1; H, 6·8%).

6-*Ethyl-2 : 4-dimethyl-1-naphthol* (I; R = Et).—m-4-*Xylyl esters of ethylsuccinic acid.* Ethylsuccinic acid was prepared by Wren and Haller's method (*J.*, 1937, 230). A mixture of xylenol (10 g.) and ethylsuccinic anhydride (12 g.), heated at 140°, yielded a solid (4·3 g.), m. p. 55—72°. This was repeatedly crystallised from benzene–light petroleum, thus affording shining prisms of a pure *ester* (1·4 g.), m. p. 84—85° (Found : C, 67·9; H, 7·3. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%).

α-*Ethyl-β(2-hydroxy-3 : 5-dimethylbenzoyl)propionic acid.* The ester (3·5 g.) in nitrobenzene (50 c.c.) was heated to 140°, and aluminium chloride (16 g.) in nitrobenzene (40 c.c.) was added during 15 minutes. The product (0·3 g.; m. p. 103—113°) was crystallised from benzene from which the required *keto-acid* (0·2 g.) was deposited as plates, m. p. 140—141° (Found : C, 67·8; H, 7·2. $C_{14}H_{18}O_4$ requires C, 67·2; H, 7·2%).

α-Ethyl-γ-(2-hydroxy-3 : 5-dimethylphenyl)butyric acid obtained from the preceding compound failed to crystallise.

6-*Ethyl-5 : 6 : 7 : 8-tetrahydro-5-keto-2 : 4-dimethyl-1-naphthol* (0·45 g.) obtained from the liquid butyric acid (0·7 g.) separated from light petroleum (b. p. 60—80°) as needles, m. p. 105—106° (Found : C, 76·9; H, 8·1. $C_{14}H_{18}O_2$ requires C, 77·1; H, 8·3%). It failed to yield a semicarbazone.

6-Ethyl-5 : 6 : 7 : 8-tetrahydro-2 : 4-dimethyl-1-naphthol (0·2 g.), obtained by reduction of the preceding compound (0·4 g.) with amalgamated zinc, was purified by sublimation and gave m. p. 61—65°. It was directly heated with selenium (0·6 g.) for 2·5 hours at 340°. The product, extracted with methanol, was first sublimed in a vacuum and then crystallised from light petroleum (b. p. 40—60°) as needles, m. p. 110—111°. Its picrate had m. p. 142° and its trinitrobenzene adduct m. p. 150°. Both derivatives and the naphthol itself were identical (mixed m. p.) with the naphthol and its corresponding derivatives obtained from desmotropo-ψ-santonin by Cocker *et al.* (*J.*, 1950, 1781).

The authors thank Mr. E. R. Stuart for the light absorption measurements, Mr. W. W. Cocker for a gift of *m*-4-xylenol (Gesellschaft für Teerverwertung m.b.H.), the Medical Research Council of Ireland for a grant, and the Egyptian Government for a grant (A. K. F.).

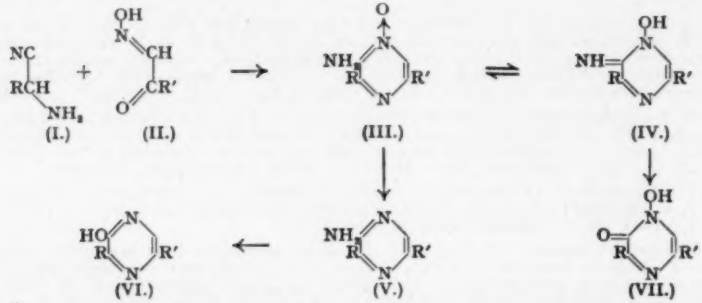
TRINITY COLLEGE, DUBLIN. [*Received, December 1st*, 1950.]

209. *Pyrazine Derivatives. Part XIII. Synthesis of 2-Aminopyrazine 1-Oxides by the Condensation of α-Amino-nitriles with Oximinomethyl Ketones.*

By WILLIAM SHARP and F. S. SPRING.

α-Amino-nitriles are shown to condense with oximinomethyl ketones to produce 3 : 5-disubstituted 2-aminopyrazine 1-oxides. This reaction affords a route to the synthesis of cyclic hydroxamic acids of the pyrazine series.

α-AMINOPROPIONITRILE (I; R = Me), liberated from its hydrochloride by the action of *N*-methylmorpholine, reacts in chloroform solution with oximinoacetone (II; R′ = Me) to form 2-amino-3 : 5-dimethylpyrazine 1-oxide (III; R = R′ = Me) [or 1 : 2-dihydro-1-hydroxy-2-imino-3 : 5-dimethylpyrazine (IV; R = R′ = Me)].



Treatment of 2-amino-3 : 5-dimethylpyrazine 1-oxide with aqueous ferric chloride gives a deep-blue colour which is discharged on addition of hydrochloric acid; in this respect it resembles 2-aminopyridine 1-oxide (Newbold and Spring, *J.*, 1949, S133). Reduction of 2-amino-3 : 5-dimethylpyrazine 1-oxide with sodium hydrosulphite (dithionite) gives 2-amino-3 : 5-dimethylpyrazine (V; R = R′ = Me) which reacts with nitrous acid to yield 2-hydroxy-3 : 5-dimethylpyrazine (VI; R = R′ = Me) identical with the product described by Dunn, Elvidge, Newbold, Ramsay, Spring, and Sweeny (*J.*, 1949, 2707).

2-Amino-3 : 5-dimethylpyrazine 1-oxide forms an acetyl derivative, a picrate, a hydrochloride, and a salt with oximinoacetone. The last compound was encountered in the course of the reaction between α-aminopropionitrile and oximinoacetone; it is readily decomposed with dilute hydrochloric acid, and oximinoacetone can then be removed by ether extraction, and 2-amino-3 : 5-dimethylpyrazine 1-oxide recovered from the aquous solution.

2-Amino-5-ethyl-3-methylpyrazine 1-oxide (III or IV; R = Me, R′ = Et) was prepared in a similar manner from α-aminopropionitrile (I; R = Me) and ethyl oximinomethyl ketone (II; R = Et) (Sharp and Spring, *J.*, 1938, 1862). This compound has similar properties to its dimethyl homologue, its aqueous solution giving the blue colour reaction with ferric chloride. Similarly 2-amino-5-methyl-3-phenylpyrazine 1-oxide (III or IV; R = Ph, R′ = Me) was prepared in low yield from α-aminophenylacetonitrile (I; R = Ph) and oximinoacetone (II; R′ = Me), and likewise 2-amino-3-methyl-5-phenylpyrazine 1-oxide (III or IV; R = Me, R′ = Ph) was obtained in low yield from α-aminopropionitrile (I; R = Me) and oximinoacetophenone (II; R′ = Ph). The efficiency of the general reaction decreases with the replacement of alkyl by aryl groups, a point which is further emphasized by our inability to obtain 2-amino-3 : 5-diphenylpyrazine 1-oxide by the condensation of α-aminophenylacetonitrile and oximinoacetophenone.

Newbold and Spring (*loc. cit.*) have shown that 2-aminopyridine 1-oxide is not hydrolysed to the corresponding cyclic hydroxamic acid, 1-hydroxy-2-pyridone, on being heated with 10% aqueous potassium hydroxide. Under similar conditions we have found likewise that 2-amino-3 : 5-dimethylpyrazine 1-oxide (III or IV; R = R′ = Me) is not hydrolysed. With stronger alkali (40%), however, and prolonged heating, a small yield of the corresponding cyclic hydroxamic

acid, 1 : 2-dihydro-1-hydroxy-2-keto-3 : 5-dimethylpyrazine (VII; R = R′ = Me) was isolated and characterised as its copper salt.

Experimental.

2-Amino-3 : 5-dimethylpyrazine 1-Oxide.—A solution of *N*-methylmorpholine (4·38 c.c., 1 mol.) in dry chloroform (30 c.c.) was shaken with α-aminopropionitrile hydrochloride (4·26 g., 1 mol.), and oximinoacetone (3·48 g., 1 mol.) quickly added. The mixture was heated under reflux for 4 hours and filtered, and the chloroform evaporated under reduced pressure. A solution of the dark-brown liquid residue in water (25 c.c.) was treated with dilute hydrochloric acid (3N.; 25 c.c.), and the mixture filtered and extracted with ether (4 × 20 c.c.) to remove excess of oximinoacetone. The aqueous solution was made alkaline (litmus) with 2N-sodium hydroxide solution and evaporated to dryness, the alkalinity being maintained by the addition of further amounts of 2N-sodium hydroxide. The solid brown residue was dried, powdered, and extracted with boiling dry benzene (200 c.c.). When the benzene was removed and the residue dried over phosphoric oxide, *2-amino-3 : 5-dimethylpyrazine 1-oxide* (2·0 g.) was obtained as felted needles, m. p. 153—154°. For analysis it was sublimed at 110°/10^{-3} mm., forming a white felted mass, m. p. 156° (Found: C, 51·8; H, 6·7; N, 30·6. $C_6H_9ON_3$ requires C, 51·8; H, 6·5; N, 30·2%). 2-Amino-3 : 5-dimethylpyrazine 1-oxide hydrate separates as needles, m. p. 76°, on spontaneous evaporation of an aqueous solution or of solutions in wet solvents such as benzene. The hydrate slowly effloresces in air and rapidly loses water over phosphoric oxide to yield the anhydrous form, m. p. 156°. A concentrated solution of the hydrate in warm benzene sets to a gelatinous mass on cooling. 2-Amino-3 : 5-dimethylpyrazine 1-oxide is readily soluble in water, ethanol, methanol, and acetic acid, less soluble in ether or benzene, and only sparingly soluble in light petroleum (b. p. 60—80°). Its aqueous solution gives a deep-blue colour with a drop of aqueous ferric chloride, the colour being discharged by a drop of dilute hydrochloric acid. Light absorption in ethanol: Maxima at 3390 A. (ε = 7400) and 2340 A. (ε = 22,000). The *picrate* separates from ethanol as small, yellow prisms, m. p. 185° (Found: C, 39·4; H, 3·1; N, 22·75. $C_6H_9ON_3,C_6H_3O_7N_3$ requires C, 39·1; H, 3·3; N, 22·8%). The *hydrochloride* separates from ether or ethanol on the addition of ethereal hydrogen chloride, and when recrystallised from ethanol (charcoal) forms needles which char above 200° without melting (Found: C, 41·2; H, 5·8; N, 23·8. $C_6H_9ON_3,HCl$ requires C, 41·0; H, 5·7; N, 23·9%). The acetyl derivative was prepared by warming 2-amino-3 : 5-dimethylpyrazine 1-oxide with acetic anhydride for 30 minutes on the water-bath. The mixture was evaporated under reduced pressure, and after being kept the crystalline product was separated and recrystallised from dioxan (charcoal) from which the *acetyl* derivative separates as plates, m. p. 228° (Found: C, 53·5; H, 6·1; N, 23·15. $C_8H_{11}O_2N_3$ requires C, 53·1; H, 6·1; N, 23·2%). It is soluble in water, the solution giving a red colour with aqueous ferric chloride.

2-Amino-3 : 5-dimethylpyrazine 1-Oxide Oximinoacetone Salt.—(*a*) The salt was isolated from the mixture obtained in the preparation of 2-amino-3 : 5-dimethylpyrazine 1-oxide as described above. The dark-brown liquid obtained after removal of the chloroform was kept overnight and the large prisms of *N*-methylmorpholine hydrochloride separated. When the filtrate was stirred, smaller crystals separated which were collected and dried to constant weight over phosphoric oxide. This solid (1 part) was refluxed with dry light petroleum, (b. p. 60—80°; 200 parts), the *oximinoacetone* salt separating on the walls of the vessel as large needles, m. p. 96°. For analysis it was recrystallised from dry benzene and dried to constant weight over phosphoric oxide at room temperature; it then had m. p. 97° (Found: C, 48·2; H, 6·2; N, 24·6. $C_9H_{14}O_3N_4$ requires C, 47·8; H, 6·2; N, 24·8%). It was characterised by reaction in aqueous solution with dilute hydrochloric acid; oximinoacetone, m. p. 62° (undepressed when mixed with an authentic specimen) was extracted with ether, and 2-amino-3 : 5-dimethylpyrazine 1-oxide, m. p. 156° (undepressed when mixed with the product described above) was isolated from the acid aqueous solution by the previously described procedure. It is soluble in water, the solution giving the blue reaction with ferric chloride.

(*b*) 2-Amino-3 : 5-dimethylpyrazine 1-oxide (70 mg.) and oximinoacetone (43 mg.) were heated to 140° for 5 minutes. The melt was cooled and the solid refluxed with light petroleum (20 c.c.; b. p. 60—80°) whereupon the salt separated as clusters of needles on the vessel walls. After being dried (P_2O_5) at room temperature it had m. p. 96°, and a recrystallisation from benzene gave the salt as needles, m. p. 97° either alone or mixed with the specimen described under (*a*).

2-Amino-3 : 5-dimethylpyrazine.—A solution of 2-amino-3 : 5-dimethylpyrazine 1-oxide (300 mg.) in water (8 c.c.) was heated under reflux with sodium hydrosulphite (dithionite) (3·5 g.) (added in 0·5-g. portions, after cooling, each ½ hour) for 4 hours. The solution was made alkaline with sodium hydroxide solution and extracted with ether (6 × 10 c.c.). The ethereal solution was dried (Na_2SO_4) and evaporated, giving 2-amino-3 : 5-dimethylpyrazine hydrate as needles, m. p. 44° (130 mg.). The hydrate was kept over phosphoric oxide and sublimed twice at 60—80°/3 × 10^{-3} mm., to yield *2-amino-3 : 5-dimethylpyrazine* as small prisms, m. p. 96° (Found: C, 58·9; H, 7·5; N, 33·7. $C_6H_9N_3$ requires C, 58·5; H, 7·4; N, 34·1%). It is soluble in water and forms the hydrate (needles; m. p. 44—45°) when crystallised from wet light petroleum. It is readily soluble in alcohol, slightly soluble in benzene, and sparingly soluble in light petroleum (b. p. 60—80°), and it does not give a blue colour with the ferric chloride reagent. The *picrate* separates from ethanol in fine needles which char above 200° and melt with decomposition at 230—240° (Found: C, 40·8; H, 3·4. $C_{12}H_{11}O_7N_6$ requires C, 40·9; H, 3·4%).

2-Hydroxy-3 : 5-dimethylpyrazine.—A solution of 2-amino-3 : 5-dimethylpyrazine (62 mg.) in N-hydrochloric acid (2 c.c.), was treated at 0° with sodium nitrite (74 mg.) added gradually during 5 minutes. The solution was left at room temperature for 2 hours, then heated for 5 minutes at 60°, cooled, neutralised with sodium hydrogen carbonate, and evaporated to dryness. The solid residue, after being dried over calcium chloride, was extracted with boiling benzene (3 × 5 c.c.). On removal of the solvent the crystalline solid (10 mg.; prisms) was sublimed at 90°/10^{-3} mm. to yield 2-hydroxy-3 : 5-dimethyl-

pyrazine, m. p. 146° (Found : N, 22·8. Calc. for $C_4H_3ON_3$: N, 22·6%); the m. p. was undepressed when the sample was mixed with a specimen prepared by Dunn, Elvidge, Newbold, Ramsay, Spring, and Sweeny (*loc. cit.*).

2-Amino-5-ethyl-3-methylpyrazine 1-*Oxide* was obtained from ethyl oximinomethyl ketone and α-aminopropionitrile hydrochloride using the procedure detailed above for the preparation of 2-amino-3 : 5-dimethylpyrazine 1-oxide, but omitting the drying procedure. *2-Amino-5-ethyl-3-methylpyrazine* 1-*oxide monohydrate* was obtained from benzene in glistening needles, m. p. 80—81° (Found : C, 49·4; H, 7·9; N, 24·7. $C_7H_{11}ON_3,H_2O$ requires C, 49·1; H, 7·7; N, 24·6%). After the hydrate had been kept over phosphoric oxide the *anhydrous base*, m. p. 109—110°, was obtained (Found : Loss in weight over P_2O_5, 10·3. $C_7H_{11}ON_3,H_2O$ requires H_2O, 10·5%). Its aqueous solution gives a blue colour with ferric chloride; this is discharged by dilute hydrochloric acid. Light absorption in ethanol: Maxima at 3370 A. (ε = 8100) and 2340 A. (ε = 28,500).

2-Amino-5-methyl-3-phenylpyrazine 1-*Oxide.*—From α-aminophenylacetonitrile hydrochloride and oximinoacetone, by use of the procedure detailed above for the preparation of 2-amino-3 : 5-dimethylpyrazine 1-oxide, a brown solid product was obtained on evaporation of the final benzene extract. This was washed with ethanol and recrystallised from the same solvent (charcoal), giving *2-amino-5-methyl-3-phenylpyrazine* 1-*oxide* as prismatic needles, m. p. 163—164° (Found : C, 65·3; H, 5·4; N, 20·95. $C_{11}H_{11}ON_3$ requires C, 65·7; H, 5·5; N, 20·9%). It was nearly insoluble in water, but readily soluble in ethanol, the solution giving a blue colour, discharged by dilute hydrochloric acid, with a drop of aqueous ferric chloride.

2-Amino-3-methyl-5-phenylpyrazine 1-*Oxide.**—Condensation of α-aminopropionitrile hydrochloride and oximinoacetophenone was effected by using the general procedure described above with the modification that the reflux time was increased to 8 hours. The chloroform solution was evaporated to dryness and the residue extracted with dilute hydrochloric acid. Examination of this extract by the ferric test failed to disclose the presence of the 2-aminopyrazine 1-oxide. The acid-insoluble solid proved to be mainly oximinoacetophenone but gave a bluish-green coloration in the ferric test indicative of the presence of the required 2-aminopyrazine 1-oxide. A solution of the solid in a slight excess of 2N-sodium hydroxide solution was evaporated, and the solid residue dried and extracted with dry boiling benzene. The gummy brown solid obtained on removing the benzene gave an intense blue colour in aqueous-ethanolic ferric chloride. Two extractions of the brown solid with light petroleum (b. p. 60—80°) removed much of the sticky impurity. The solid was crystallised from acetone (charcoal) and heated at $100°/2 \times 10^{-6}$ mm. for 1 hour. The residue was crystallised from ethanol, giving *2-amino-3-methyl-5-phenylpyrazine* 1-*oxide* as prisms, m. p. 188—189°. For analysis it was sublimed at $150°/10^{-4}$ mm.; it then had m. p. 189° (Found : N, 21·1. $C_{11}H_{11}ON_3$ requires N, 20·9%). A solution of 2-amino-3-methyl-5-phenylpyrazine 1-oxide in ethanol gives a deep blue colour with ferric chloride, discharged by dilute hydrochloric acid.

1 : 2-*Dihydro*-1-*hydroxy*-2-*keto*-3 : 5-*dimethylpyrazine.*—2-Amino-3 : 5-dimethylpyrazine 1-oxide (1 g.) in water (4 c.c.) was treated with a solution of sodium hydroxide (4 g.) in warm water (1·5 c.c.). A yellow solid separated and the mixture was heated under reflux in an oil-bath at 140° for 22 hours, during which time ammonia was evolved. The cold mixture was diluted with water, nearly neutralized with hydrochloric acid, and evaporated to dryness. The alkaline solid residue was dried, powdered, and extracted with dry chloroform (3 × 30 c.c.) to remove unchanged 2-amino-3 : 5-dimethylpyrazine 1-oxide. The residue was dissolved in water, and the solution adjusted to pH 4 with hydrochloric acid and evaporated to dryness, additions of hydrochloric acid being made at intervals to maintain the pH at 4·0. The solid residue was dried, powdered, and extracted with dry chloroform (3 × 30 c.c.). Removal of the solvent gave an orange-brown solid (300 mg.) which on sublimation at $140°/5 \times 10^{-3}$ mm. gave 1 : 2-dihydro-1-hydroxy-2-keto-3 : 5-dimethylpyrazine, m. p. 124—126°, not depressed when mixed with a specimen, m. p. 135°, prepared by Dunn, Elvidge, Newbold, Ramsay, Spring, and Sweeny (*loc. cit.*). The compound gave an acid reaction with litmus, effervesced with sodium hydrogen carbonate solution, and gave an intense wine-red colour in aqueous or alcoholic solution with ferric chloride solution. It was characterised by conversion into its copper salt. A solution (pH 4·0) of the crude hydroxamic acid (300 mg.) in hydrochloric acid was treated with saturated aqueous cupric acetate solution, and the green precipitate was filtered off, washed, dried (250 mg.), and crystallised twice from hot dioxan (1 : 200) to yield the *copper salt* of 1 : 2-dihydro-1-hydroxy-2-keto-3 : 5-dimethylpyrazine as tufts of prismatic needles, which charred without melting at *ca.* 275° (Found : C, 42·0; H, 4·1; N, 16·8. $C_{14}H_{14}O_4N_4Cu$ requires C, 42·2; H, 4·1; N, 16·4%). A solution of the salt in dioxan gives an orange-red colour with aqueous ferric chloride solution.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, December 9th*, 1950.]

* This experiment was made by Miss Sheila M. Gray, B.Sc.

210. *Triterpene Resinols and Related Acids. Part XX. Conversion of α-Amyrin into* iso-α-*Amyranone* (12-*Ketoursane*).

By JOHN MCLEAN, G. A. SILVERSTONE, and F. S. SPRING.

α-Amyrin has been converted into α-amyranedione, reduction of which by the Wolff–Kishner method gives *iso*-α-amyranone (12-ketoursane) and not the required saturated hydrocarbon of the α-amyrin series. *iso*-α-Amyranone is also obtained from α-amyrene by oxidation with hydrogen peroxide followed by rearrangement of the intermediate oxide.

THE experiments described in this paper were undertaken with the object of preparing α-amyrane (ursane), the parent hydrocarbon of the α-amyrin triterpenoid sub-group, which was required for comparison with β-amyrane (oleanane), the corresponding hydrocarbon of the β-amyrin sub-group.

According to Seymour, Sharples, and Spring (*J.*, 1939, 1075) oxidation of α-amyrin benzoate with hydrogen peroxide gives as major product a compound, $C_{37}H_{54}O_3$, which was considered to be α-amyranonyl benzoate since on reduction with sodium and amyl alcohol it gave a saturated diol, α-amyranediol, and on treatment with bromine an αβ-unsaturated ketone, *iso*-α-amyrenonyl benzoate. We find that this compound (m. p. 217—219°, $[\alpha]_D$ +132°) is isomerised by treatment with hydrochloric acid–acetic acid to give a benzoate, m. p. 227—229°, $[\alpha]_D$ +25°. Treatment of the isomeric compounds, m. p. 217—219° and m. p. 227—229°, with bromine in acetic acid gives in each case bromo-α-amyranonyl benzoate and thence *iso*-α-amyrenonyl benzoate (Seymour and Spring, *J.*, 1941, 319). Reduction of the two isomers with sodium and amyl alcohol yields α-amyranediol. Either the two isomers must be isomeric α-amyranonyl benzoates, differing in orientation around the asymmetric centre produced during the oxidation, or the compound, m. p. 217—219°, is α-amyrin benzoate oxide which when treated with mineral acid rearranges to α-amyranonyl benzoate, this rearrangement also occurring during bromination. In either case the compound, m. p. 227—229°, is α-amyranonyl benzoate; it has been characterised by hydrolysis to α-amyrananol and by the preparation of an enol acetate.

A decision between the two possible structures for the compound, m. p. 217—219°, is difficult because of the inert character of the carbonyl group in amyranonyl esters and the relative ease with which it is isomerised to α-amyranonyl benzoate, m. p. 227—229°. A decision by means of ultra-violet absorption spectroscopy is not feasible since benzoates are not good subjects for the measurement of low-intensity selective absorptive. Attempts were therefore made to obtain the acetate corresponding to the benzoate, m. p. 217—219°.

Ruzicka, Jeger, Redel, and Volli (*Helv. Chim. Acta*, 1945, **28**, 199) have reported that treatment of α-amyrin acetate with ozone gives α-amyrin acetate oxide, m. p. 204—205°, $[\alpha]_D$ +139°, which on treatment with hydrochloric acid is isomerised to α-amyranonyl acetate, m. p. 259—260°, $[\alpha]_D$ +15·6°, showing a low-intensity absorption maximum at 2600 A. We find that treatment of α-amyrin acetate with hydrogen peroxide gives as major product α-amyrin acetate oxide, $C_{32}H_{52}O_3$, m. p. 207—209°, $[\alpha]_D$ +114°, which does not exhibit carbonyl absorption in the ultra-violet region. When treated with hydrochloric acid it gives the saturated ketone, α-amyranonyl acetate, m. p. 282—284°, $[\alpha]_D$ +11°, showing a low-intensity absorption maximum at 2820 A., and characterised by the preparation of an enol acetate. The melting point of this ketone is considerably higher than that observed by Ruzicka, Jeger, Redel, and Volli (*loc. cit.*) using an open capillary; a mixture of α- and β-amyranonyl acetates shows a depressed melting point. Hydrolysis of α-amyranonyl acetate yields α-amyrananol, identical with that obtained from α-amyranonyl benzoate, and treatment of α-amyranonyl acetate with bromine gives *iso*-α-amyrenonyl acetate.

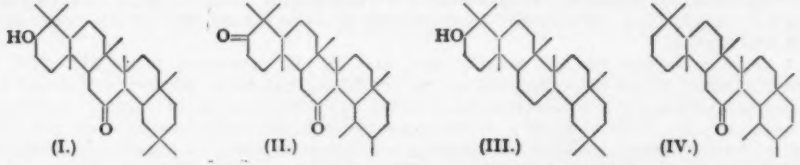
The appreciable difference in the optical rotation of the acetate oxide prepared by means of hydrogen peroxide (+114°) and that obtained by Ruzicka, Jeger, Redel, and Volli by using ozone (+139°), led us to repeat the latter preparation. By using a 2·5% ozone–oxygen mixture α-amyrin acetate was converted into α-amyrin acetate oxide which had properties (m. p. 208—210°, $[\alpha]_D$ +111°) closely agreeing with those of the hydrogen peroxide product.

The compound, $C_{37}H_{54}O_3$, m. p. 217—219°, obtained by hydrogen peroxide oxidation of α-amyrin benzoate has been identified as α-amyrin benzoate oxide by correlating it with α-amyrin acetate oxide. Whereas vigorous alkaline hydrolysis of the benzoate oxide followed by acetylation of the product gives α-amyranonyl acetate, mild alkaline hydrolysis yields a product which on acetylation gives α-amyrin acetate oxide. Furthermore treatment of

α-amyrin benzoate with ozone gives α-amyrin benzoate oxide with properties similar to those of the hydrogen peroxide product.

The α-amyrin ester oxides are extremely unstable; they are isomerised in part to the corresponding α-amyranonyl esters in alkaline and in acid media. Furthermore the isomerisation of the ester oxides to the saturated ketones is not a simple process. Thus in the case of α-amyrin benzoate oxide rearrangement by means of mineral acid gives α-amyranonyl benzoate, m. p. 227—229°, $[\alpha]_D$ +25°, in approximately 50% yield. From the mother liquors was obtained an isomeric compound, m. p. 232—236°, $[\alpha]_D$ +88°, which on bromination gives bromo-α-amyranonyl benzoate identical with that obtained by bromination of either α-amyranonyl benzoate or α-amyrin benzoate oxide. Similar behaviour has been encountered in the purification of the related ketone derived from methyl acetylursolate, and Dreiding, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1950, **33**, 1325) report that purification of this compound is best effected by simple crystallisation since attempted purification by chromatographic methods led to the partial formation of two isomeric compounds.

Oxidation of α-amyranonol with chromic anhydride gives α-amyranedione. Reduction of this diketone by the Wolff–Kishner method gave *iso*-α-amyranone and not the required saturated hydrocarbon, α-amyrane. *iso*-α-Amyranone has been obtained by an alternative route from α-amyrene, itself prepared by the Wolff–Kishner and Clemmensen methods from α-amyrenone (cf. Winterstein and Stein, *Annalen*, 1933, **502**, 223; Ruzicka, Müller, and Schellenberg, *Helv. Chim. Acta*, 1939, **22**, 758). Treatment of α-amyrene with hydrogen peroxide gives α-amyrene oxide which when treated with hydrochloric acid gives *iso*-α-amyranone, identical with the ketone obtained by partial reduction of α-amyranedione. Reduction of α-amyrene oxide with sodium and amyl alcohol yields a secondary alcohol *iso*-α-amyranol, characterised as its acetyl derivative. Attempts were made to convert *iso*-α-amyranol into the corresponding chloride with the object of reducing the latter to the required α-amyrane. These attempts were unsuccessful, treatment of *iso*-α-amyranol with thionyl chloride, phosphoryl chloride, phosphorus pentachloride, or dry hydrogen chloride giving α-amyrene in each case.



(I.) (II.) (III.) (IV.)

These experiments emphasise the major difference in reactivity between the α- and the β-amyrin series. In the case of the β-amyrin group the Wolff–Kishner reduction of β-amyranonol proceeds smoothly to give β-amyranol (Ruzicka and Jeger, *Helv. Chim. Acta*, 1941, **24**, 1178). This difference finds expression in the formulæ adopted by Ruzicka, Jeger, and their collaborators for α- and β-amyrins, according to which β-amyranonol (2-hydroxy-12-keto-oleanane) is (I) and α-amyranedione (2 : 12-diketoursane) is (II), reduction of the former giving β-amyranol (2-hydroxyoleanane) (III) from which the parent hydrocarbon oleanane can readily be obtained, whilst reduction of the latter gives *iso*-α-amyranone (12-ketoursane) (IV). The inert character of the carbonyl group in *iso*-α-amyranone can be attributed to the steric effect of the methyl group attached to $C_{(19)}$.

Experimental.

(Optical rotations were measured in chloroform solution in a 10-cm. tube; m. p.s are uncorrected.)

α-Amyrin Benzoate Oxide.—(*a*) α-Amyrin benzoate (10 g.) was oxidised as described by Seymour, Sharples, and Spring (*loc. cit.*). The hot reaction mixture was treated with water until turbid. The crystalline solid separating on cooling was collected and repeatedly recrystallised from benzene–methanol, giving *α-amyrin benzoate oxide* (5 g.) as fine needles, m. p. 217—219°, $[\alpha]_D^{16}$ +132° (*c*, 2·9), (Found: C, 81·7; H, 9·6. $C_{37}H_{54}O_3$ requires C, 81·3; H, 10·0%).

(*b*) A solution of α-amyrin benzoate (2·5 g.) in dry, freshly distilled carbon tetrachloride (50 c.c.) was treated with ozonised oxygen (2·5%) for 7 hours; the mixture then gave no colour with tetranitromethane. The solution was evaporated and the residue extracted with benzene. The extract was washed with dilute sodium hydroxide which extracted a small amount of acidic product. The washed benzene solution was evaporated and the residue crystallised from chloroform–methanol giving α-amyrin benzoate oxide as needles (1·5 g.), m. p. 215—217°, $[\alpha]_D^{16}$ +130° (*c*, 3·0), undepressed when mixed with the specimen described above.

(*c*) A solution of α-amyrin benzoate (1·0 g.) in glacial acetic acid (75 c.c.) was treated at 100° with a solution of potassium permanganate (0·24 g.) in water (8 c.c.), added during 30 minutes with stirring

The mixture was heated for 2 hours and then diluted with water, and the product isolated by means of ether. Crystallisation from alcohol gave α-amyrin benzoate oxide (0·2 g.), m. p. 217—219° undepressed when mixed with the specimen described at (*a*).

α-Amyrin Acetate Oxide.—(*a*) Oxidation of α-amyrin acetate (10 g.) with hydrogen peroxide was carried out as described for the benzoate. The crude reaction product (5·0 g.) separated from chloroform–methanol as plates, m. p. 207—209°, $[\alpha]_D^{17}$ +105° (*c*, 1·6). Fractional crystallisation from alcohol gave a main fraction (2·0 g.), m. p. 203—205°, $[\alpha]_D^{19}$ +118° (*c*, 3·5). Purification of this by chromatography on alumina gave in small yield *α-amyrin acetate oxide* as blades, m. p. 207—209°, $[\alpha]_D^{20}$ +114° (*c*, 2·3) (Found: C, 79·3; H, 10·5. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). The oxide does not show low-intensity carbonyl absorption in the ultra-violet.

(*b*) Treatment of α-amyrin acetate with 2·5%-ozonised oxygen as described for the benzoate gave α-amyrin acetate oxide as small blades, m. p. 208—210°, $[\alpha]_D^{17}$ +111° (*c*, 3·1), from aqueous acetone (Found: C, 79·6; H, 10·7%).

α-Amyranonyl Benzoate.—Rearrangement of α-amyrin benzoate oxide was effected in chloroform–acetic acid solution using concentrated hydrochloric acid as employed by Ruzicka, Jeger, Redel, and Volli (*loc. cit.*). The product was crystallised from chloroform–methanol, giving *α-amyranonyl benzoate* as plates, m. p. 227—229°, $[\alpha]_D^{17}$ +24·7° (*c*, 2·0) (Yield 50%) (Found: C, 81·0; H, 10·2. $C_{37}H_{54}O_3$ requires C, 81·3; H, 10·0%).

α-Amyranonyl acetate was obtained in 60% yield by similar rearrangement of α-amyrin acetate oxide. It separated from chloroform–methanol as plates, m. p. 280—282°, $[\alpha]_D$ +11·4° (*c*, 1·6) (Found: C, 79·1; H, 10·7. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%). α-Amyranonyl acetate showed an absorption maximum at 2820 A. (ε = 225).

α-Amyranonol.—α-Amyranonyl benzoate (1 g.) was refluxed for 2 hours with an excess of 1% alcoholic potassium hydroxide. The mixture was diluted with water, and the product isolated by means of benzene. It was crystallised from light petroleum (b. p. 60—80°), giving *α-amyranonol* as fern-like growths of fine needles, m. p. 218—220°, $[\alpha]_D$ −5° (*c*, 1·5) (Found: C, 81·1; H, 10·9. $C_{30}H_{50}O_3$ requires C, 81·4; H, 11·4%). Acetylation of α-amyranonol with acetic anhydride and pyridine at room temperature gave α-amyranonyl acetate as plates (from chloroform–methanol), m. p. 280—282°, $[\alpha]_D$ +9° (*c*, 2·9), undepressed when mixed with the specimen described above.

Enol Acetate of α-Amyranonyl Acetate.—A solution of α-amyranonyl acetate (3 g.) in acetic anhydride (60 c.c.), containing freshly fused sodium acetate (3 g.), was refluxed for 24 hours. The mixture was treated with water, and the product crystallised from alcohol, giving the enol *acetate* as needles, m. p. 255—257°, $[\alpha]_D^{17}$ +49° (*c*, 2·6) (Found: C, 77·6; H, 10·1. $C_{34}H_{54}O_4$ requires C, 77·5; H, 10·3%).

The enol *acetate* of α-amyranonyl benzoate was prepared similarly from α-amyranonyl benzoate. It separated from aqueous acetone as blades, m. p. 220—222°, $[\alpha]_D^{14}$ +65° (*c*, 7·4) (Found: C, 79·7; H, 9·3. $C_{39}H_{56}O_4$ requires C, 79·3; H, 9·8%).

Bromo-α-amyranonyl Benzoate.—This was obtained in approximately 70% yield by bromination of either α-amyranonyl benzoate or α-amyrin benzoate oxide, as described by Seymour and Spring (*loc. cit.*). It separated from chloroform–methanol as blades, m. p. 186—188° (decomp.), $[\alpha]_D^{17}$ +27° (*c*, 2·4) (Found: C, 71·1; H, 8·8. Calc. for $C_{37}H_{55}O_3Br$: C, 70·8; H, 8·8%). Treatment of the bromoketone with hydrogen bromide in acetic acid (Seymour and Spring, *loc. cit.*) and treatment of either α-amyranonyl benzoate or α-amyrin benzoate oxide with bromine as described by Seymour, Sharples, and Spring (*loc. cit.*) gave *iso*-α-amyrenonyl benzoate as prisms, m. p. 212—214°, $[\alpha]_D$ +91° (*c*, 2·0), from benzene–alcohol (Found: C, 81·7; H, 9·7. Calc. for $C_{37}H_{52}O_3$: C, 81·6; H, 9·6%).

iso-α-Amyrenonyl Acetate.—This was obtained by direct bromination of α-amyranonyl acetate as described for the preparation of the corresponding benzoate by Seymour, Sharples, and Spring; solid did not separate during the reaction. *iso*-α-Amyrenonyl acetate separated as plates, m. p. 284—286° (decomp.), $[\alpha]_D^{18}$ +83° (*c*, 1·9), from benzene–methanol.

Hydrolysis of either *iso*-α-amyrenonyl acetate or benzoate with alcoholic potassium hydroxide gave *iso*-α-amyrenonol as fine needles, m. p. 241—242°, $[\alpha]_D^{18}$ +72° (*c*, 2·0), +75° (*c*, 2·15), from aqueous alcohol (Found: C, 82·0; H, 11·1. Calc. for $C_{30}H_{48}O_3$: C, 81·8; H, 11·0%).

α-Amyranediones.—A solution of α-amyranonol (1 g.) in acetic acid (17 c.c.) was treated at room temperature with a solution of chromic anhydride (0·22 g.) dissolved in a minimum of water and diluted with acetic acid (3 c.c.). Next morning the mixture was diluted with water, and the product isolated by means of ether. The ether solution was washed with dilute sodium hydroxide and then with water, and dried (Na_2SO_4). Acidification of the alkaline washings gave a trace of acidic material. The neutral fraction was crystallised from aqueous alcohol, giving *α-amyranedione* as needles, m. p. 166—168°, $[\alpha]_D$ +2° (*c*, 2·4) (Found: C, 82·0; H, 10·9. $C_{30}H_{48}O_3$ requires C, 81·8; H, 11·0%). α-Amyranedione was also obtained by similar oxidation of α-amyranediol.

α-Amyrene.—A mixture of α-amyrenone (6 g.), sodium ethoxide (from 6 g. of sodium and 150 c.c. of ethanol), and hydrazine hydrate (90%; 18 c.c.) was heated in an autoclave at 180° for 18 hours. The mixture was diluted with water and extracted with ether. The ether solution was washed, dried (Na_2SO_4), and evaporated, giving a yellow oil which quickly solidified. Crystallisation of the solid from ethanol gave α-amyrene as plates (3·5 g.), m. p. 109—111°, $[\alpha]_D^{20}$ +93° (*c*, 1·75) (Found: C, 88·1; H, 12·4. Calc. for $C_{30}H_{50}$: C, 87·7; H, 12·3%). Treatment of α-amyrenone semicarbazone with sodium ethoxide as described by Ruzicka, Müller, and Schellenberg (*loc. cit.*) gave α-amyrene (40% yield) as plates (from ethanol), m. p. 109—111°, $[\alpha]_D^{18}$ +93° (*c*, 2·4). Similarly, reduction of α-amyrenone with amalgamated zinc in hydrochloric acid–acetic acid solution, as described by Winterstein and Stein (*loc. cit.*), gave α-amyrene as plates (from alcohol), m. p. 109—111°, $[\alpha]_D$ +92° (*c*, 2·0).

Ruzicka, Müller, and Schellenberg (*loc. cit.*) obtained α-amyrene from α-amyrenone semicarbazone by the Wolff–Kischner process as plates, m. p. 124°, $[\alpha]_D$ +95°. Although the rotation is in good

agreement with that found by us for all the preparations described above, there is an appreciable difference in melting point. Attempts were therefore made to obtain a higher-melting specimen of α-amyrene. A specimen, m. p. 110—112°, prepared by reduction of α-amyrenone with hydrazine and sodium ethoxide, was filtered through a column of alumina (Grade II). After crystallisation from methanol–ether it had m. p. 112—113°. It was again filtered through a 5′ column of alumina (Grade I), giving three fractions which, after crystallisation from ether–methanol, gave α-amyrene as plates, m. p. 111—113°, 111·5—113°, and 111·5—113°, respectively. A similar behaviour was observed (*a*) after chromatography of a specimen of α-amyrene prepared from α-amyrenone semicarbazone by Wolff–Kishner reduction, the final product being obtained as plates, m. p. 111·5—113°, and (*b*) by using a specimen of α-amyrene obtained by Clemmensen reduction of α-amyrenone; after chromatography this specimen was obtained as plates, m. p. 111·5—113°, from ether–methanol.

α-Amyrene was recovered unchanged after shaking it for 6 hours in ethyl acetate with hydrogen at 50 atm. pressure, in the presence of platinum catalyst.

α-*Amyrene Oxide*.—α-Amyrene (5 g.) was oxidised with hydrogen peroxide under the conditions employed for the oxidation of α-amyrin benzoate. When the reaction mixture cooled α-amyrene (0·5 g.) separated and was collected. The acetic acid solution was diluted with water, and the product isolated by means of benzene. After the solution had been washed the benzene was removed, giving a gum (3·8 g.) which was dissolved in light petroleum–benzene (1 : 1), and the solution filtered through a short column of alumina. The solvent was removed from the filtrate yielding a colourless oil which rapidly crystallised. Recrystallisation from alcohol gave α-*amyrene oxide* as plates, m. p. 116—118°, $[\alpha]_D^{21}$ +135° (*c*, 2·0) (Found: C, 84·5; H, 11·9. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%).

iso-α-*Amyranone* (12-*Ketoursane*).—(*a*) Isomerisation of α-amyrene oxide with hydrochloric acid in chloroform–acetic acid gave iso-α-*amyranone* as blades, m. p. 150—152°, $[\alpha]_D^{24}$ ±0° (*c*, 0·7), from aqueous alcohol (Found: C, 84·1; H, 11·6. $C_{30}H_{50}O$ requires C, 84·4; H, 11·8%). *iso*-α-Amyranone crystallised from alcohol in a solvated form, m. p. 141—143°, which after being dried at 120° in a vacuum gave the non-solvated form.

(*b*) A mixture of α-amyranedione (0·75 g.), sodium ethoxide (from 0·75 g. of sodium and 30 c.c. of ethanol), and hydrazine hydrate (90%; 3·5 c.c.) was heated in an autoclave for 18 hours at 180°. The product isolated in the usual manner gave in low yield *iso*-α-amyranone, m. p. 141—143° undepressed when mixed with the specimen described above.

iso-α-*Amyranol*.—A boiling solution of α-amyrene oxide (2·8 g.) in amyl alcohol (38 c.c.) was treated with sodium (2·8 g.), and the mixture refluxed for 20 minutes. Sodium (2·8 g.) was again added and the mixture refluxed for 2½ hours. A small quantity of alcohol was added, the mixture boiled with water, and the amyl alcohol removed in steam. The product was isolated by means of ether and crystallised from aqueous acetone or alcohol, giving iso-α-*amyranol* (1·5 g.) as plates, m. p. 178—180°, $[\alpha]_D^{20}$ +48·1° (*c*, 2·1) (Found: C, 84·0; H, 12·25. $C_{30}H_{52}O$ requires C, 84·0; H, 12·2%).

Conversion of iso-α-*Amyranol into* α-*Amyrene*.—(*a*) The alcohol (0·6 g.) was heated under reflux with thionyl chloride (5 c.c.) for 30 minutes. (*b*) A solution of *iso*-α-amyranol (0·3 g.) in dry ether (20 c.c.) was saturated below 5° with dry hydrogen chloride and kept overnight at 0°. (*c*) A solution of *iso*-α-amyranol in phosphoryl chloride (5 c.c.) was kept overnight at room temperature. In each case the sole product isolated was α-amyrene, m. p. and mixed m. p. 109—111°.

iso-α-*Amyranyl acetate* was obtained by acetylation of the alcohol with pyridine and acetic anhydride at room temperature. It separates from alcohol as blades, m. p. 244—246° (Found: C, 81·1; H, 11·9. $C_{32}H_{54}O_2$ requires C, 81·6; H, 11·6%).

The award of a Maintenance Grant (to G. A. S.) by the Department of Scientific and Industrial Research is gratefully acknowledged.

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, December 15th*, 1950.]

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211. *Preliminary Syntheses in the Morphine Series. Part III.* Michael Condensations with 2-Arylcyclohex-2-enones and Cyclisation of the Products to Octahydrophenanthrene Derivatives.*

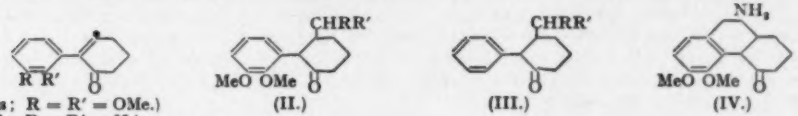
By DAVID GINSBURG and RAPHAEL PAPPO.

Products formed by Michael condensation of 2-aryl*cyclo*hex-2-enones with compounds containing reactive methylene groups are described. The transformation of these products into various octahydrophenanthrene derivatives has been studied.

IN Part II of this series (*J.*, 1951, 516) the preparation of 2-aryl*cyclo*hex-2-enones was described. For their further conversion into pharmacologically active compounds related to morphine, it was necessary to substitute 2-(2 : 3-dimethoxyphenyl)*cyclo*hex-2-enone (I*a*) at position 3 (marked •) with a radical which would form the 9 : 10-bridge in the desired phenanthrene system and still retain reactive groups on which further transformations could be based.

* A preliminary report covering part of the material contained in this communication is being published: Pappo and Ginsburg, *Bull. Res. Council Israel*, 1951, **1**, in the press.

A satisfactory solution of this problem lies in the observation that 2-(2 : 3-dimethoxyphenyl)-*cyclo*hex-2-enone undergoes Michael condensation with compounds containing reactive methylene groups, giving high yields of adducts of type (II), *e.g.*, (II; R = CO_2Et or CN, R′ = CO_2Et) with ethyl malonate and ethyl cyanoacetate, respectively. A compound such as (II; R = NO_2, R′ = CO_2Me) is obviously a precursor of an octahydrophenanthrene carrying an amino-group in the 10- and a keto-group in the 4-position (IV). 2-Phenyl*cyclo*hex-2-enone (I*b*) was used as a model substance in the study of this condensation.



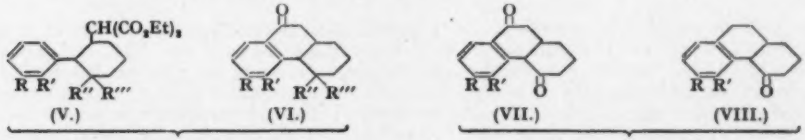
(I*a*; R = R′ = OMe.) (I*b*; R = R′ = H.) (II.) (III.) (IV.)

Only compounds containing a reactive methylene group condensed with the 2-aryl*cyclo*hex-2-enones. Attempted condensation with compounds containing a methine group, such as the ethyl diethoxymethylmalonate or phthalimidomalonate, failed, although compounds of this type are known to take part in Michael condensations in other cases (cf. the use of ethyl acetamido- and formamido-malonate in syntheses of amino-acids; Albertson and Archer, *J. Amer. Chem. Soc.*, 1945, **67**, 2043; Snyder, Shekleton, and Lewis, *ibid.*, p. 310; Galat, *ibid.*, 1947, **69**, 965). These failures may perhaps be attributed to the presence of the bulky 2-aryl groups. Such " steric hindrance " of the Michael condensation is not without analogy. Thus, Turner and Voitle (*ibid.*, 1950, **72**, 4166, where also previous literature is cited) have shown that 1-acetyl-2-methyl*cyclo*hexene does not undergo Michael condensation with *cyclo*hexanone, and Woods (*ibid.*, 1947, **69**, 2551; cf. Koelsch, *ibid.*, 1945, **67**, 569) has recorded an analogous observation for 5 : 5-dimethyl-3-phenyl*cyclo*hex-2-enone.

The progress of the Michael condensation can be followed qualitatively by treating one drop of the reaction liquid with 2 : 4-dinitrophenylhydrazine solution : the 2 : 4-dinitrophenylhydrazone of the αβ-unsaturated starting material is red or orange-red, that of the end-product yellow to orange.

The Michael condensation products obtained with ethyl malonate have been systematically investigated with a view to determining conditions for the cyclisation to octahydrophenanthrene derivatives.

(i) Malonic esters (II and III; R = R′ = CO_2Et), or their ketals, were reduced by the Clemmensen method to malonic esters of type (V*a* and *b*), and the latter were hydrolysed and cyclised by means of zinc chloride in acetic acid–acetic anhydride (but not by hydrogen fluoride) to yield, through simultaneous half-decarboxylation, the corresponding 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-9-ketophenanthrenes (VI*a* and *b*). Equally, Clemmensen reduction of 3-keto-2-phenyl*cyclo*hexylacetic acid which was available from (III; R = R′ = CO_2Et) led to the corresponding known *trans*-2-phenyl*cyclo*hexylacetic acid which could easily be cyclised to Cook's *trans*-octahydroketophenanthrene (VI*b*), m. p. 95° (Cook, Hewett, and Robinson, *J.*, 1939, 168; cf. Linstead *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 2014).



(V.) (VI.) (VII.) (VIII.)

a; R = R′ = OMe; R″ = R‴ = H.
b; R = R′ = R″ = R‴ = H.
c; R = R′ = OMe; R″ = OH; R‴ = H.

a; R = R′ = OMe.
b; R = R′ = H.

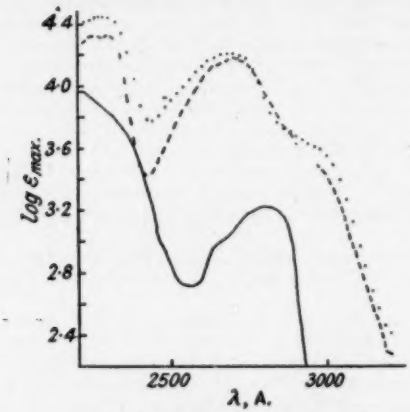
(ii) Hydrogenation of (II; R = R′ = CO_2Et) in presence of Adams's catalyst gave the corresponding carbinol, which, on hydrolysis and cyclisation as in (i) was converted into the 4-acetoxy-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-9-keto-5 : 6-dimethoxyphenanthrene (acetate of VI*c*).

(iii) When the carbonyl group in (II, III; R = R′ = CO_2Et) was blocked by formation of the ketal with ethylene glycol (Salmi, *Ber.*, 1938, **71**, 1803; cf. Sulzbacher, Bergmann, and Pariser, *J. Amer. Chem. Soc.*, 1948, **70**, 2827) or with ethyl orthoformate, the ester groups could be

subjected to alkaline hydrolysis and the free acid cyclised. By hydrolysis of the ketal groups, compounds (VII*a* and *b*) were then obtained. This detour proved necessary in this case when it became apparent that compounds of types (II) and (III) are unstable to alkali, the Michael condensation being reversed.

The two carbonyl groups in a compound such as (VII*a* or *b*) differ greatly in reactivity. Thus, the 4-keto-group could be selectively converted into a ketal and catalytic reduction attacked preferentially the 9-carbonyl group, reducing it to a methylene group (as in VIII*a* and *b*). Significant differences in the rate of formation of ketals between arylaliphatic and alicyclic ketones have been observed before (acetophenone is much less reactive than 2-methyl*cyclo*hexanone; Sulzbacher, Bergmann, and Pariser, *loc. cit.*), and the complete de-oxygenation of carbonyl groups conjugated with aromatic nuclei by catalytically activated hydrogen is not uncommon (cf. Horning and Reisner, *J. Amer. Chem. Soc.*, 1949, **71**, 1036; Linstead, Whetstone and Levine, *ibid.*, 1942, **64**, 2014).

The ultra-violet spectra illustrate this difference between the two carbonyl groups rather strikingly (see figure). The 9-ketone (VI*a*) and the 4-(ethylene glycol) ketal of the corresponding 4 : 9-diketone (VII*a*) have identical spectra which resemble that of 3 : 4-dimethoxybenzoic acid (Hirshberg, Lavie, and E. Bergmann, *J.*, 1951, in the press). The wave-length of the first band reflects the interference with resonance, exerted by the "*ortho*-substituent" to the 9-carbonyl



Ultra-violet absorption, in isooctane, *of:*

------, 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-9-*keto*-5 : 6-*dimethoxyphenanthrene*;
. . . . . , 4-(*ethylene glycol*) *ketal of* 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketo*-5 : 6-*dimethoxyphenanthrene*;
———, 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4-*keto*-5 : 6-*dimethoxyphenanthrene*.

group (cf., for the spectrum of 3 : 4-dimethoxyacetophenone, Tasaki, *Chem. Zentr.*, 1927, II, 1949). 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-Octahydro-4-keto-5 : 6-dimethoxyphenanthrene (VIII*a*) has only one band of lower intensity; its extinction coefficient, however, is much higher than that of a normal aliphatic ketone, probably owing to superposition, on the carbonyl band, of the absorption of the veratrole system which absorbs approximately at the same wave-length as non-aromatic, non-conjugated ketones (for the spectrum of veratrole, cf. Savard, *Bull. Soc. chim.*, 1928, **43**, 1073; Kiss *et al.*, *ibid.*, 1949, 275; Wolf and Herold, *Z. physikal. Chem.*, 1931, *B*, **13**, 201. For the spectrum of 2-phenyl*cyclo*hexanone, cf. Bachmann and Wick, *J. Amer. Chem. Soc.*, 1950, **72**, 3388, and Alpen, Kumler, and Strait, *ibid.*, 1950, **72**, 4558, who also give a theoretical interpretation of this type of spectrum).

The following table summarises these results; it indicates, incidentally, that in the cases of (VI*a*) and the ketal of (VII*a*), the solvent has little effect on the absorption of these—highly substituted—compounds.

As far as our experience shows, the Michael condensation and subsequent cyclisation leads to only one of the possible isomers—presumably of analogous configuration in all cases. Even (II; R = CN, R′ = CO_2Et) resulted in 90% yield although in this compound there is an

additional—however, easily enolised—asymmetric carbon atom in the side chain. It should, of course, be borne in mind that the alkaline medium necessary for the Michael condensation may well cause isomerisation of $C_{(13)}$ so that the configuration of the product isolated does not necessarily reflect the steric mechanism of the addition reaction. As judged by the formation

Ultra-violet absorption.

Compound.	Solvent.	$\lambda_{max.}$	log $\varepsilon_{max.}$	$\lambda_{max.}$	log $\varepsilon_{max.}$
(VI*a*)	*iso*Octane	2700	4·18	2300	4·34
,, ...	Dioxan	2720	4·11	2320	4·26
,, ...	Ethanol (anhyd.)	2780	4·10	2320	4·17
(VII*a* ketal)	*iso*Octane	2680	4·21	2270	4·45
,, ...	Dioxan	2740	4·16	2280	4·33
,, ...	Ethanol (anhyd.)	2780	4·29	2300	4·41
(VIII*a*)	*iso*Octane	2780—2880	3·21	—	—

of *trans*-octahydro-9-ketophenanthrene (VI*b*) from (III; R = R′ = CO_2Et), the two alicyclic rings in the octahydrophenanthrene ultimately isolated are locked in the *trans*-configuration.

A noteworthy case, in which the Michael condensation was used to prepare a precursor of a hydrophenanthrene derivative, is the condensation of 1-acetyl*cyclo*hexene with *cyclo*hexanone in the presence of sodamide (Rapson and Robinson, *J.*, 1935, 1285). The compound obtained, 9-keto-Δ^{10}-dodecahydrophenanthrene, may be viewed as resulting (i) from Michael condensation, followed by (ii) cyclodehydration of the adduct. Linstead *et al.* (*J.*, 1939, 842, 850; *J. Amer. Chem. Soc.*, 1942, **64**, 2003, 2009) have shown that reduction of this ketone yields a product which can be oxidised to *trans-anti-trans*-diphenic acid, and, therefore, also contains in *trans*-configuration the two rings which are hydroaromatic in the compounds described in the present communication.

Work on the stereochemistry of the new substances is now in progress with a view to obtaining the configuration prevalent in the morphine system, in which the ethanamine bridge and the hydrogen at $C_{(14)}$ are believed (but not proved) to be *cis* to each other (Grewe, *Naturwiss.*, 1946, **33**, 333; Schöpf and Pfeiffer, *Annalen*, 1930, **483**, 157).

Experimental.

(All m. p.s and b. p.s are uncorrected.)

*A. Michael Condensation with 2-Aryl*cyclo*hex-2-enones* (I).—*Ethyl* 2-(2 : 3-*dimethoxyphenyl*)-3-*keto*cyclo*hexylmalonate* (II; R = R′ = CO_2Et). A mixture of the 2-aryl*cyclo*hex-2-enone (I) (0·1 mole), ethyl malonate (0·2 mole), and 20% sodium ethoxide solution (0·025 mole) was kept at 60° for 3 hours, then overnight at room temperature. Acetic acid (1·5 ml., 0·025 mole) was added, and the mixture diluted with ether (200 ml.). The ethereal solution was washed with water, then dried, and the solvent evaporated. Unchanged ethyl malonate was removed in a high vacuum (bath-temp. below 120° at 0·1 mm.). The remaining oil (yield, about 95%) was sufficiently pure for further transformations; in larger batches decomposition occurs on distillation but a small sample of the *ester* (II; R = R′ = CO_2Et) can be purified by distillation at 0·1 mm. (bath. temp. 220°) (Found: C, 64·4; H, 7·5. $C_{21}H_{28}O_7$ requires C, 64·3; H, 7·2%). It forms a 2 : 4-*dinitrophenylhydrazone*, yellow crystals, m. p. 117—119° (from ethanol) (Found: C, 56·7; H, 5·6; N, 10·0. $C_{27}H_{32}O_{10}N_4$ requires C, 56·6; H, 5·6; N, 9·8%).

Analogously, the following substances were prepared: *Ethyl* 3-*keto*-2-*phenyl*cyclo*hexylmalonate* (III; R = R′ = CO_2Et), an oil (Found: C, 68·6; H, 7·2. $C_{19}H_{24}O_5$ requires C, 68·7; H, 7·2%); 2 : 4-*dinitrophenylhydrazone*, yellow crystals, m. p. 119—120° (from ethanol) (Found: C, 58·5; H, 5·7; N, 11·2. $C_{25}H_{28}O_9N_4$ requires C, 58·6; H, 5·5; N, 10·9%).

Ethyl α-*cyano*-α-2-(2 : 3-*dimethoxyphenyl*)-3-*keto*cyclo*hexylacetate* (II; R = CN, R′ = CO_2Et), m. p. 95° (from butanol) (yield, 90%) (Found: C, 66·4; H, 6·2; N, 4·4. $C_{19}H_{25}O_5N$ requires C, 66·0; H, 6·7; N, 4·1%); 2 : 4-*dinitrophenylhydrazone*, yellow crystals, m. p. 176—178° (from ethanol–chloroform) (Found: C, 56·9; H, 5·3; N, 13·4. $C_{25}H_{27}O_8N_5$ requires C, 57·1; H, 5·1; N, 13·3%).

Methyl 2-(2 : 3-*dimethoxyphenyl*)-3-*keto*cyclo*hexylmalonate*, an oil (97%) (Found: C, 62·1; H, 6·5. $C_{19}H_{24}O_7$ requires C, 62·6; H, 6·6%); 2 : 4-*dinitrophenylhydrazone*, orange crystals, m. p. 162—163° (from ethyl acetate–ethanol) (Found: C, 55·0; H, 5·4; N, 10·9. $C_{25}H_{28}O_{10}N_4$ requires C, 55·1; H, 5·2; N, 10·3%).

Methyl α-*cyano*-α-2-(2 : 3-*dimethoxyphenyl*)-3-*keto*cyclo*hexylacetate*, m. p. 114° (from butanol) (95%) (Found: C, 65·3; H, 6·2; N, 4·6. $C_{19}H_{23}O_5N$ requires C, 65·3; H, 6·3; N, 4·2%); 2 : 4-*dinitrophenylhydrazone*, yellow crystals, m. p. 167° (from ethanol–chloroform) (Found: C, 56·2; H, 5·0; N, 13·7. $C_{25}H_{27}O_8N_5$ requires C, 56·4; H, 4·9; N, 13·7%).

Methyl α-*cyano*-α-(3-*keto*-2-*phenyl*cyclo*hexyl*)*acetate*, m. p. 86—87° (from butanol) (Found: C, 70·4; H, 6·2; N, 5·1. $C_{16}H_{17}O_3N$ requires C, 70·8; H, 6·3; N, 5·2%); 2 : 4-*dinitrophenylhydrazone*, yellow crystals, m. p. 155—157° (from ethanol–ethyl acetate) (Found: C, 58·4; H, 4·6; N, 15·8. $C_{22}H_{21}O_6N_5$ requires C, 58·5; H, 4·6; N, 15·5%).

3-*Nitromethyl*-2-*phenyl*cyclo*hexanone* (III; R = NO_2, R′ = H). A mixture of 2-phenyl*cyclo*hex-2-enone (0·1 mole), nitromethane (0·2 mole), and a 30% methanolic solution of Triton B methoxide

(equivalent to 0·025 mole) was kept at 60° for 3 hours and then at room temperature overnight. Acetic acid (0·025 mole) was added, followed by ether (200 ml.), whereupon the *product* crystallised in 80% yield. It showed a m. p. of 126·5—127·5° (from dioxan–ethanol) (Found: C, 67·0; H, 6·6; N, 6·1. $C_{13}H_{15}O_5N$ requires C, 66·9; H, 6·4; N, 6·0%) and gave a 2 : 4-*dinitrophenylhydrazone*, yellow crystals, m. p. 155—157° (from ethanol–chloroform) (Found: C, 55·1; H, 4·4; N, 16·8. $C_{19}H_{19}O_8N_5$ requires C, 55·2; H, 4·6; N, 16·9%).

When sodium methoxide was used as condensing agent, a slightly less pure product was formed in 80% yield.

Methyl 2-(2 : 3-*dimethoxyphenyl*)-3-*keto*cyclo*hexyl*-α-*nitroacetate* (II; R = NO_2, R′ = CO_2Me). The condensation, using methyl nitroacetate (0·2 mole), was carried out as above for 12 hours at 60°. The ethereal solution of the product was washed with water and dilute sodium hydrogen carbonate solution, which removed most of the unchanged ester; the balance was distilled off in a high vacuum. The oily residue (90%) was sufficiently pure for further transformations. Similarly was obtained methyl 3-keto-2-phenyl*cyclo*hexyl-α-nitroacetate (III; R = NO_2, R′ = CO_2Me) (90%), an oil.

The last two adducts were reduced to the corresponding amino-esters, and then hydrolysed to the amino-acids. Their further transformations will be reported later.

B. Cyclisation of the Michael Adducts: Method (i).—trans-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-9-*ketophenanthrene* (VI*b*). (*a*) A mixture of ethyl 3-keto-2-phenyl*cyclo*hexylmalonate (III; R = R′ = CO_2Et) (10 g.), anhydrous ethanol (30 g.), ethyl orthoformate (30 g.), and toluene-*p*-sulphonic acid (0·1 g.) was refluxed for 4 hours. The solution was cooled, neutralised with sodium methoxide, and concentrated *in vacuo* (water-pump). The residual oil was refluxed with 50% aqueous potassium hydroxide solution (20 ml.) for 4 hours. The solution was diluted with water, neutralised with hydrochloric acid to slightly alkaline reaction (pH *ca.* 8), and extracted with ether to remove unhydrolysed ester and some phenolic material. It was then acidified with excess of hydrochloric acid and kept for 1 hour (for completion of the hydrolysis of the acetal grouping), and the oil which separated was taken up in ether. By removal of the solvent, 7·5 g. of crude, oily 3-keto-2-phenyl*cyclo*hexylmalonic acid were obtained. It was not possible to isolate the ketal of this acid.

(*b*) Clemmensen reduction (Martin's modification, *J. Amer. Chem. Soc.*, 1936, **58**, 1438). The crude malonic acid (3·5 g.) and amalgamated zinc wool (7 g.) were added to a mixture of water (5 ml.), concentrated hydrochloric acid (12 ml.), and toluene (7 ml.), and the whole was refluxed for 48 hours with addition of concentrated hydrochloric acid (3·5 ml.) at 6-hour intervals. The product was then extracted with benzene, the benzene solution washed with water, and the solvent evaporated off. The oily solid was recrystallised from dilute acetic acid and *trans*-2-phenyl*cyclo*hexylacetic acid, m. p. 110°, obtained (2·8 g.) (Found: C, 77·4; H, 8·6. Calc. for $C_{14}H_{18}O_2$: C, 77·1; H, 8·3%) (Linstead *et al.*, *J. Amer. Chem. Soc.*, 1942, **64**, 2019, report m. p. 113·5—114·5°). The acid could be further purified by distillation in a high vacuum.

(*c*) Cyclisation. The crude product (2 g.) of the Clemmensen reduction in concentrated sulphuric acid was heated on the steam-bath for 10 minutes (Cook, Hewett, and Lawrence, *J.*, 1936, 71), poured on ice, and extracted with ether. The extract was washed with dilute sodium carbonate solution, then dried, and the solvent removed. The residue (1·7 g.) crystallised and melted at 92—95°. After recrystallisation from ethanol, 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-octahydro-9-ketophenanthrene melted at 95° (Cook *et al.*, *loc. cit.*, report m. p. 95°) (Found: C, 84·3; H, 7·9. Calc. for $C_{14}H_{14}O$: C, 84·0; H, 8·0%) (yield 70%). It formed an *oxime*, m. p. 176° (from ethanol) (Cook *et al.*, *loc. cit.*, report m. p. 175—177°), and a 2 : 4-*dinitrophenylhydrazone*, orange crystals, m. p. 265° (decomp.) (precipitated from ethanol, washed with hot ethanol–ethyl acetate) (Found: N, 14·5. $C_{20}H_{20}O_4N_4$ requires N, 14·7%).

Alternatively the ester (III; R = R′ = CO_2Et) was reduced by the Clemmensen–Martin method, the product hydrolysed with aqueous potassium hydroxide, and the resultant malonic acid decarboxylated at 180—200° (10 minutes). From 15 g. of ester were thus obtained 8 g. of crude *trans*-2-phenyl-*cyclo*hexylacetic acid.

1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-9-*keto*-5 : 6-*dimethoxyphenanthrene* (VI*a*). (*a*) Reduction of (II*a*): Ethyl 2-(2 : 3-dimethoxyphenyl)-3-keto*cyclo*hexylmalonate (22·5 g.) was reduced, as described above, by the Martin modification of the Clemmensen method. The crude oily residue weighed 16·5 g.

(*b*) Hydrolysis. The product (16·5 g.) was refluxed with 50% aqueous potassium hydroxide solution (35 ml.) for 4 hours, and the mixture diluted with water, extracted with ether, and acidified with hydrochloric acid. The precipitated oil was taken up in ether. Removal of the solvent yielded a semi-solid mass (15 g.) consisting of a mixture of the malonic and acetic acid derivatives. Crystallisation of 1·8 g. from ether yielded 0·8 g. of 2-(2 : 3-*dimethoxyphenyl*)cyclo*hexylmalonic acid*, m. p. 195—196° (decomp.) (Found: C, 63·6; H, 6·8. $C_{17}H_{22}O_6$ requires C, 63·3; H, 6·8%).

(*c*) Cyclisation. The crude mixture (13 g.) of acetic and malonic acid derivatives was dissolved in a mixture of glacial acetic acid (78 ml.) and acetic anhydride (52 ml.). Fused zinc chloride (1·04 g.) was added and the whole heated under reflux for 75 minutes. To the hot solution was added water (300 ml.) at a rate which maintained boiling. The oil, which separated, crystallised on storage. The solid was collected, washed with cold water, and dried. The *ketone* (VI*a*) melted at 96—97° (from aqueous–ethanol) (yield, 9·6 g., 65% from II*a*) (Found: C, 73·6; H, 8·2. $C_{14}H_{16}O_3$ requires C, 73·8; H, 7·7%), and formed a 2 : 4-*dinitrophenylhydrazone*, crimson crystals, m. p. 248° (decomp.) (from ethanol–ethyl acetate) (Found: N, 12·5. $C_{22}H_{24}O_6N_4$ requires N, 12·7%). This ketone is perhaps identical with the product, m. p. 86—89° (corr.) (dinitrophenylhydrazone, m. p. 237—238°), described by Hornung, Hornung, and Platt (*J. Amer. Chem. Soc.*, 1947, **69**, 2929).

Cyclisation of the Michael Adducts: Method (ii).—*Ethyl* 2-(2 : 3-*dimethoxyphenyl*)-3-*hydroxy*cyclo*hexylmalonate* (V*c*). The compound (II; R = R′ = CO_2Et) (10 g.) in 95% ethanol (100 ml.) was hydrogenated in the presence of Adams's catalyst (0·5 g.) at room temperature and 60 lbs./sq. in. After 3

hours, 1 mole of hydrogen had been absorbed. The catalyst was removed by filtration and the solvent removed *in vacuo*. The residual (Vc) was an oil (9·8 g.). Its *acetate*, prepared by means of glacial acetic acid, acetic anhydride, and fused zinc chloride, had m. p. 83—84° (from methyl*cyclo*hexane) (Found: C, 63·6; H, 7·6. $C_{22}H_{32}O_8$ requires C, 63·3; H, 7·3%).

1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-4-*hydroxy*-9-*keto*-5 : 6-*dimethoxyphenanthrene* (VIc). (*a*) The foregoing oily hydroxy-ester (10 g.) was refluxed with 50% aqueous potassium hydroxide (30 ml.) for 1 hour. As part of the potassium salt separated out, water (75 ml.) was added and the refluxing was continued for 4 hours. The mixture was cooled and extracted with ether, and the aqueous layer just acidified with 18% hydrochloric acid and boiled for a few minutes, whereupon the oil which had separated began to crystallise. 2-(2 : 3-*Dimethoxyphenyl*)-3-*hydroxy*cyclo*hexylmalonic acid* was washed with a small volume of ice-water (6 g.) and recrystallised from dioxan–methyl*cyclo*hexane. It had m. p. 185° (decomp.) (Found: C, 59·7; H, 6·5. $C_{17}H_{22}O_7$ requires C, 60·3; H, 6·5%).

(*b*) Cyclisation. The acid (2 g.) and fused zinc chloride (0·20 g.) were added to a mixture of acetic acid (12 ml.) and acetic anhydride (10 ml.), and the whole was refluxed for 1·75 hours. The oily product obtained as above crystallised partly after being scratched (1·6 g.). Recrystallisation from ethanol gave 4-*acetoxy*-1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-9-*keto*-5 : 6-*dimethoxyphenanthrene* (0·7 g.), m. p. 129° (Found: C, 67·7; H, 6·9. $C_{18}H_{22}O_6$ requires C, 67·9; H, 6·9%); its 2 : 4-*dinitrophenylhydrazone* formed crimson crystals, m. p. 263° (decomp.) (from ethanol–ethyl acetate) (Found: N, 11·1. $C_{24}H_{26}O_9N_4$ requires N, 11·2%).

(*c*) Hydrolysis of the acetate. The above acetate (0·5 g.) was refluxed for 90 minutes with a mixture of 10% aqueous sodium hydroxide solution (2 ml.) and ethanol (2 ml.). After acidification and evaporation *in vacuo*, the residue was taken up in ether, and the extract washed with alkali. Trituration of the residue with methyl*cyclo*hexane gave crystals of 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4-*hydroxy*-9-*keto*-5 : 6-*dimethoxyphenanthrene* (VIc) (0·32 g.), m. p. 97·5—98° (from methyl*cyclo*hexane–benzene) (Found: C, 69·5; H, 7·3. $C_{16}H_{20}O_4$ requires C, 69·6; H, 7·3%), which gave a 2 : 4-*dinitrophenylhydrazone*, crimson crystals, m. p. 238—240° (decomp.) (from ethanol–ethyl acetate) (Found: N, 12·3. $C_{22}H_{24}O_7N_4$ requires N, 12·3%).

Cyclisation of the Michael Adducts: *Method* (iii).—1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-4 : 9-*diketo*-5 : 6-*dimethoxyphenanthrene* (VII*a*). (*a*) The ketal was prepared by treating ethyl 2-(2 : 3-dimethoxyphenyl)-3-keto*cyclo*hexylmalonate (10 g.) with anhydrous ethanol (30 g.), ethyl orthoformate (30 g.), and toluene-*p*-sulphonic acid (0·1 g.) as described above. After hydrolysis 2-(2 : 3-*dimethoxyphenyl*)-3-*keto*cyclo*hexylmalonic acid* crystallised as the hemihydrate after one month. It melted at 98—100° (decomp.) after recrystallisation from water, the m. p. being dependent on the rate of heating (Found: C, 58·9; H, 6·6. $C_{17}H_{22}O_7,\frac{1}{2}H_2O$ requires C, 59·1; H, 6·1%).

(*b*) Cyclisations. (i) The anhydrous 2-(2 : 3-dimethoxyphenyl)-3-keto*cyclo*hexylmalonic acid (15 g.) and fused zinc chloride (1·34 g.) were added to a mixture of glacial acetic acid (93 ml.) and acetic anhydride (65 ml.), and the whole was refluxed for 75 minutes. Water (400 ml.) was added to the hot mixture and, after cooling, the oil which separated was taken up in ether. The ethereal extract was washed with dilute sodium hydroxide solution and the solution evaporated to 30 ml. After prolonged storage, a solid, m. p. 105—110°, crystallised and was filtered off (3 g.). The remaining oil was refluxed for 90 minutes with potassium hydroxide (1·8 g.) in water (30 ml.). After 12 hours, a second crop of the above product had crystallised; it was filtered off and washed with a small amount of cold ether, and had m. p. 110° (7 g.). After recrystallisation from ethanol, the 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*octahydro*-4 : 9-*diketo*-5 : 6-*dimethoxyphenanthrene* (VII*a*) had m. p. 115° (Found: C, 70·1; H, 6·6. $C_{16}H_{18}O_4$ requires C, 70·0; H, 6·5%); it gave a *dioxime*, m. p. 210° (decomp.) (from ethanol) (Found: N, 9·2. $C_{16}H_{20}O_4N_2$ requires N, 9·2%).

(ii) 2-(2 : 3-Dimethoxyphenyl)-3-keto*cyclo*hexylmalonic acid hydrate (16 g.) was decarboxylated at 200° (10 minutes), and the resulting product dissolved in anhydrous hydrogen fluoride (50 g.). After evaporation of the hydrogen fluoride, water was added and the product extracted with ether. The extract was washed with 5% potassium hydroxide solution, then dried, and the solvent removed. The diketone (VII*a*) crystallised readily, m. p. 115° (from ethanol) (yield, 90%).

(iii) The ethylene glycol ketal (see below) of 2-(2 : 3-dimethoxyphenyl)-3-keto*cyclo*hexylmalonic acid (6 g.) was decarboxylated at 190—200° (10 minutes). The crude product was heated with 80% sulphuric acid (24 ml.) on the steam-bath for 30 minutes. The mixture was poured on ice, and the solid washed with dilute aqueous ammonia, and then recrystallised from ethanol (yield, 2 g.; m. p. 115°).

1 : 2 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-4 : 9-*diketophenanthrene* (VII*b*). (*a*) A mixture of ethyl 2-phenyl-3-keto*cyclo*hexylmalonate (III; R = R′ = CO_2Et) (7 g.), ethylene glycol (15 ml.), benzene (30 ml.), and toluene-*p*-sulphonic acid (0·1 g.) was refluxed for 6 hours, the water being removed azeotropically. The oily residue, obtained as above, was refluxed for 4 hours with 50% aqueous potassium hydroxide (14 g.), and the reaction product diluted with water. After acidification to pH 8, the mixture was extracted with ether, cooled, and covered with benzene (30 ml.), and an equivalent amount of hydrochloric acid was added dropwise with stirring and cooling. The ketal-acid was precipitated, but passed at once into the benzene layer. The aqueous phase was separated and extracted once more with benzene. The combined benzene extracts were dried. When scratched the (*ethylene glycol*) *ketal* of 2-phenyl-3-keto*cyclo*hexylmalonic acid crystallised (5·5 g.), m. p. 175—176° (decomp.) (from toluene–dioxan) (Found: C, 63·6; H, 6·4. $C_{17}H_{20}O_6$ requires C, 63·7; H, 6·3%).

(*b*) Cyclisation. The above ketal (10 g.) was decarboxylated at 180—200° (10 minutes). The residue was dissolved in concentrated sulphuric acid and the solution heated on the steam-bath for 10 minutes. It was then poured on ice and extracted with ether; the extract was washed with water and dilute sodium carbonate solution, then dried, and the solvent removed. The residual oily *diketone* (VII*b*) crystallised on storage (5·5 g., 75%), m. p. 94—95° (from butanol) (Found: C, 78·5; H, 6·6. $C_{14}H_{14}O_2$ requires C,

78·5; H, 6·5%). It gave a *dioxime*, m. p. 235° (decomp.) (from ethanol) (Found : N, 11·9. $C_{14}H_{16}O_3N_2$ requires N, 11·5%).

Experiments with Methyl α-Cyano-α-2-(2 : 3-dimethoxyphenyl)-3-ketocyclohexylacetate.—Alkaline hydrolysis. (*a*) This ester was converted into the *ketal* with ethylene glycol as described for (VII*b*) (yield, 80%), the product melting at 139—140° (from butanol) (Found : C, 63·8; H, 6·7; N, 4·0. $C_{20}H_{25}O_6N$ requires C, 64·0; H, 6·7; N, 3·7%). The ketal was hydrolysed by 5% hydrochloric acid at 80° (3 hours).

(*b*) Hydrolysis. The above ketal (10 g.) was refluxed with potassium hydroxide (15 g.) in butanol (50 ml.) until evolution of ammonia ceased (*ca.* 10 hours). After addition of water (50 ml.), refluxing was continued for 30 minutes. The aqueous alkaline layer was separated and the butanol layer washed once with water. The combined aqueous extracts were washed with ether, acidified to pH *ca.* 8, filtered to remove a small quantity of precipitate, and covered with benzene (100 ml.). Hydrochloric acid was added with cooling and stirring, so that the precipitate formed was immediately taken up by the benzene. The benzene extract was quickly removed, washed with water, and when scratched and cooled deposited a voluminous precipitate of the *ethylene glycol ketal* (80%) of 2-(2 : 3-dimethoxyphenyl)-3-ketocyclohexylmalonic acid; this melted at 182—183° (decomp.) (from benzene–dioxan) (Found : C, 59·8; H, 5·9. $C_{19}H_{24}O_8$ requires C, 60·0; H, 6·3%). Decarboxylation was effected in quantitative yield at 190—200° in 10 minutes.

This ketal is identical with the ethylene glycol ketal of the malonic acid prepared by hydrolysis of (II; R = R′ = CO_2Et).

Experiments with Ethyl α-Cyano-α-2-(2 : 3-dimethoxyphenyl)-3-ketocyclohexylacetate.—(*a*) *Alkaline hydrolysis.* (i) Without blocking of the carbonyl group. To this ester (II; R = CN, R′ = CO_2Et) (1 g.), in ethanol (5 ml.) was added 5% sodium hydroxide solution (30 ml.). After 24 hours, crystals of 2-(2 : 3-dimethoxyphenyl)*cyclo*hex-2-enone (I*a*), m. p. 96° (from butanol), had formed by reversal of the Michael condensation.

(ii) With blocking of the carbonyl group. The ketal from the ester (20 g.) was dissolved in ethanol (150 ml.), and a solution of potassium hydroxide (3·25 g.) in ethanol (40 ml.) added. After 3 hours at room temperature the solution, which was neutral to litmus, was concentrated *in vacuo*, water (100 ml.) was added, and some unhydrolysed starting material extracted with ether. The aqueous layer was then acidified with concentrated hydrochloric acid (10 ml.), and the oil which separated taken up in ether. The oily residue of *α-cyano-α-2-(2 : 3-dimethoxyphenyl)-3-keto-cyclohexylacetic acid* crystallised after scratching (15 g.), m. p. 163—165°, decomp. at 170° (from 30% acetic acid) (Found : C, 63·9; H, 6·4; N, 4·4. $C_{17}H_{19}O_5N$ requires C, 64·3; H, 6·0; N, 4·4%).

Attempted cyclisations of the product with acetic acid–acetic anhydride–zinc chloride or with hydrogen fluoride were unsuccessful.

(*b*) *Reduction.* The ester (20 g.) in 95% ethanol (200 ml.) absorbed 1 mole of hydrogen in the presence of Adams's catalyst (0·5 g.) at room temperature and 60 lbs./sq. in. during 4 hours. The catalyst was removed by filtration and the solvent removed *in vacuo*. The oily residue was dissolved in ether, and the solution washed with dilute hydrochloric acid to remove basic material (350 mg.) Evaporation of the ether yielded the oily ethyl α-cyano-α-2-(2 : 3-dimethoxyphenyl)-3-hydroxy*cyclo*hexylacetate (18·5 g.).

Hydrolysis was effected with dilute ethanolic potassium hydroxide at room temperature as described above for the hydrolysis of the ketal. The oily product could not be cyclised with acetic acid–acetic anhydride–zinc chloride; under these conditions *α-cyano-α-3-acetoxy-2-(2 : 3-dimethoxyphenyl)cyclohexylacetic acid* was obtained, m. p. 115° (from dilute acetic acid) (Found : N, 3·9. $C_{19}H_{23}O_6N$ requires N, 3·9%).

Attempted cyclisation of the acetate with anhydrous hydrogen fluoride was also unsuccessful.

C. Differences in Reactivity of the Keto-groups in (VII).—1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-4-*keto*-5 : 6-*dimethoxyphenanthrene* (VIII*a*). The diketone (VII*a*) (9 g.) in 95% ethanol (100 ml.) absorbed 2 moles of hydrogen in the presence of 5% palladium–charcoal (0·5 g.) at room temperature and 60 lbs./sq. in. during 1 hour. The catalyst was removed by filtration and the solvent removed *in vacuo*. 1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-4-*keto*-5 : 6-*dimethoxyphenanthrene*, m. p. 104—105° (from ethanol), was thus obtained in nearly quantitative yield (8·5 g.) (Found : C, 73·6; H, 7·6. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%). This reduction could also be carried out in glacial acetic acid at 60°. The 2 : 4-*dinitrophenylhydrazone*, orange crystals, had m. p. 183—184° (from ethanol–ethyl acetate) (Found : C, 60·1; H, 5·3; N, 12·6. $C_{22}H_{24}O_6N_4$ requires C, 60·0; H, 5·5; N, 12·7%), the *oxime* m. p. 148—149° (from ethanol) (Found : C, 70·4; H, 7·4; N, 5·5. $C_{16}H_{21}O_3N$ requires C, 70·0; H, 7·6; N, 5·1%), and the *semicarbazone* m. p. 219—221° (decomp.) (from ethanol) (Found : N, 13·4. $C_{17}H_{23}O_3N_3$ requires N, 13·2%).

Partial Clemmensen reduction of the diketone yielded the same product.

1 : 2 : 3 : 4 : 9 : 10 : 11 : 12-*Octahydro*-4-*ketophenanthrene* (VIII*b*). The diketone (VII*b*) (2 g.), hydrogenated in glacial acetic acid (100 ml.) in the presence of 10% palladium–charcoal (0·2 g.) at 60—70° and 60 lbs./sq. in., absorbed 2 moles of hydrogen during 90 minutes. After removal of the catalyst and evaporation of the solvent, the 4-*monoketone* was obtained as an oil (1·8 g.). On cooling it crystallised, m. p. 48—49° (from methanol) (Found : C, 84·2; H, 8·0. $C_{14}H_{16}O$ requires C, 84·0; H, 8·0%). It gave a 2 : 4-*dinitrophenylhydrazone*, yellow crystals, m. p. 193—194° (from ethanol–chloroform) (Found : N, 14·5. $C_{20}H_{20}O_4N_4$ requires N, 14·7%), and a *semicarbazone*, m. p. 219° (from butanol) (Found : N, 15·8. $C_{15}H_{19}ON_3$ requires N, 16·3%).

Selective ketalisation of the 4-keto-group. (i) A mixture of the diketone (VII*a*) (7 g.), ethylene glycol (15 ml.), benzene (30 ml.), and toluene-*p*-sulphonic acid (0·2 g.) was heated for 3 hours, the water liberated being removed azeotropically. The mixture was cooled and neutralised with sodium methoxide, the benzene layer separated, and the glycol layer diluted with water and extracted with benzene. The

combined benzene extracts were washed with water and the solvent was removed *in vacuo*. The 4-(*ethylene glycol*) *ketal* crystallised immediately, m. p. 134—135° (from ethanol) (Found: C, 67·9; H, 7·0. $C_{16}H_{22}O_4$ requires C, 67·9; H, 6·9%).

(ii) The diketone (VII*b*) similarly gave a 4-(*ethylene glycol*) *ketal*, m. p. 89° (from hexane) (admixture with the diketone gave a large depression) (Found: C, 74·3; H, 7·3. $C_{16}H_{18}O_3$ requires C, 74·4; H, 7·0%).

The authors are indebted to Dr. Y. Hirshberg of this Institute for the ultra-violet-absorption data. This paper represents part of a thesis submitted by Raphael Pappo to the Hebrew University, Jerusalem, in partial fulfilment of the requirements for the degree of Ph.D.

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212. *Some Considerations on the Strengths of Hybrid Bonds in Excited States of the Hydrogen Molecule-ion.*

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The potential-energy curves for a series of defined states of H_2^+ are calculated by the molecular-orbital method. The results are compared with those of a similar study by Pauling and Sherman, from which the present work differs in that the correct H atom eigenfunctions are used in place of the approximate Slater eigenfunctions.

The calculated ratio of 1 : 3 : 4 obtained by Pauling and Sherman for the relative strengths of *s*–*s*, *p*–*p* and sp^3–sp^3 bonds in the 2- and 3-quantum states of H_2^+ is not found from the results of this paper.

Calculations on the ground state of H_2^+ show that the description of this state as a 1*s*–2*p* hybrid ($Z = 1$) gives a very close approximation in respect of the energy, but the calculated bond length is too small, and the calculated force constant too large. The additional variation in Z (Dickinson) corrects the error in r_e.

An examination of Badger's rule ($k_e^{-\frac{1}{3}} \propto r_e$) applied to the calculated constants for the different states of H_2^+ shows that the rule is followed rather closely when states of similar bonding are considered as a class.

AN important postulate of the quantum-mechanical theory of directed valence, as developed in a simple way by Slater (*Phys. Review*, 1931, **38**, 1109) and Pauling (*J. Amer. Chem. Soc.*, 1931, **53**, 1367), is that the relative "bond-forming power" of an orbital is proportional to the magnitude of the angular part of the orbital along the bond axis. According to this postulate, the "bond-forming powers" of *s*-, *p*-, and sp^3-orbitals of a given atom stand in the ratio $1 : \sqrt{3} : 2$, corresponding to a 1 : 3 : 4 ratio between the strengths of *s*–*s*, *p*–*p*, and sp^3–sp^3 bonds formed by the atom. In their paper "A Quantitative Discussion of Bond Orbitals," Pauling and Sherman (*J. Amer. Chem. Soc.*, 1937, **59**, 1450) sought to verify this simple postulate by a calculation (using the method of molecular orbitals) of the strengths of the 1-electron bond in various hypothetical states of the H_2^+ molecule-ion. They obtained the ratio 1 : 2·7 : 4·1 for the order of the strengths of the 2-quantum *s*–*s*, *p*–*p*, and sp^3–sp^3 bonds in H_2^+, in good agreement with the expected 1 : 3 : 4 ratio.

The quantitative treatment of hybridization by Pauling and Sherman makes several simplifying assumptions. For reasons explained in their paper, Pauling and Sherman chose to use the approximate Slater wave-functions in constructing molecular orbitals describing excited states of the H_2^+ molecule-ion. The use of these approximate atomic orbitals required other, and more drastic, approximations in the subsequent evaluation of the energy integrals.

We have thought it of interest to re-examine the problem, following essentially the procedure of Pauling and Sherman, except that we use the correct H atom eigenfunctions throughout, and thus avoid all approximations except the general one of the L.C.A.O. method, *i.e.*, the approximation involved in representing the molecular orbitals by some linear combination of atomic orbitals.

Excited States of H_2^+: *2-Quantum States.*—We consider the 1-electron bonding in various hypothetical states of H_2^+, presumed to be derived from a proton and an *excited* H atom. Representing the molecular orbitals by

$$\psi = c(\phi_a + \phi_b) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (1)$$

where ϕ_A and ϕ_B are similar atomic orbitals for the atoms A and B, the case of $2s$–$2s$ bonding requires that ϕ_A and ϕ_B be $2s$ atomic orbitals, and the case of $2p$–$2p$ bonding correspondingly that ϕ_A and ϕ_B are $2p_z$ orbitals. The $2s$, $2p_z$ orbitals are known precisely for the H atom, *viz.*:

$$\phi_A^s = \sqrt{\frac{\beta^3}{\pi}} \cdot (1 - \beta r_A) e^{-\beta r_A} \quad \ldots \quad (2)$$

$$\phi_A^z = \sqrt{\frac{\beta^5}{\pi}} \cdot r_A \cos\theta_A \, e^{-\beta r_A} \quad \ldots \quad (3)$$

$$\beta = Z/2a_0 \quad \ldots \quad (4)$$

The potential-energy curves ($Z = 1$) calculated for s–s and p–p bonding with equations (1), (2), and (3) are shown by curves *A* and *B* of Fig. 1. Curve *C* of the same figure represents the most stable *hybrid* arising from the interaction of states A and B. The eigenfunction ψ_h representative of the hybrid state C is given by:

$$\psi_h = a\psi_I + b\psi_{II} \quad \ldots \quad (5)$$

where ψ_I describes state A, and ψ_{II} describes state B. Curve *C* corresponds to values of the mixing coefficients a, b in equation (5) which minimize the energy integral $\int \psi_h H \psi_h d\tau$ at each value of the internuclear separation.

FIG. 1.
2-Quantum States of H_2^+.

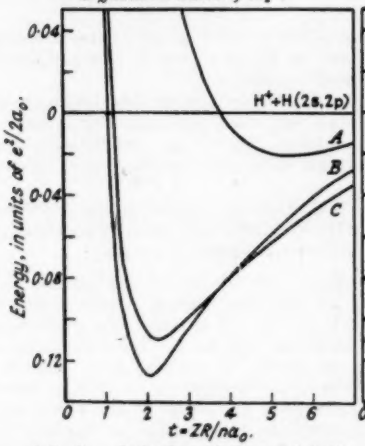
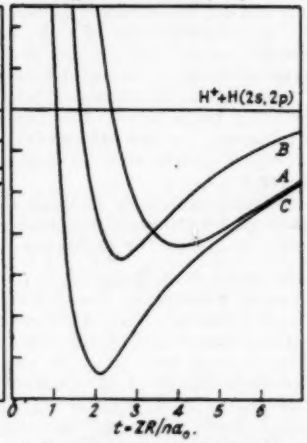


FIG. 2.
2-Quantum States of H_2^+.



A, 2s–2s. *B*, 2p–2p. *C*, *Best* sp-*hybrid*. *A*, *B*, sp^3-*Hybrids*. *C*, *Best* sp-*hybrid*.

There are both qualitative and quantitative differences between the curves in Fig. 1 and the corresponding curves calculated by Pauling and Sherman. The numerical differences—expressed in terms of the calculated dissociation energies D_e, and equilibrium distances r_e—are summarized in Table I. The D_e values are measured in units $e^2/2a_0$ ($e^2/2a_0$ = ionization potential of normal H atom), and the r_e values are in atomic units (*i.e.*, units of a_0 = Bohr radius = 0·529 A.).

TABLE I.

Calculated constants in excited states of H_2^+.

Bond.	D_e (this paper).	r_e.	D_e (P. and S.).	r_e.
$2s$–$2s$	0·0207	10·72	0·040	7·8
$2p$–$2p$	0·1094	4·58	0·108	4·6
Best s–p hybrid	0·1272	4·10	0·170	4·72

The qualitative differences between the curves in Fig. 1 and the Pauling–Slater curves are most apparent in case of curve *C* and its counterpart. The differences originate in the nodeless character of the Slater 2s atomic orbital, compared with the nodal function (equation 2). Thus

the Pauling–Sherman analogue of curve *C* corresponds at all distances to positive values for the ratio a/b of the mixing coefficients a, b of equation (5), whereas curve *C* reflects a reversal in sign of a/b in the region $t = 3{\cdot}7$ ($t = ZR/na_0$).

The point is perhaps emphasized more clearly by Fig. 2. In this we have plotted energy for the sp^3-bonded H_2^+ molecule. These are the states described by the molecular orbital

$$\psi_{sp^3} = c(\phi_A^{sp^3} + \phi_B^{sp^3}) \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (6)$$

where $\phi_A^{sp^3}$ is a hybrid atomic orbital,

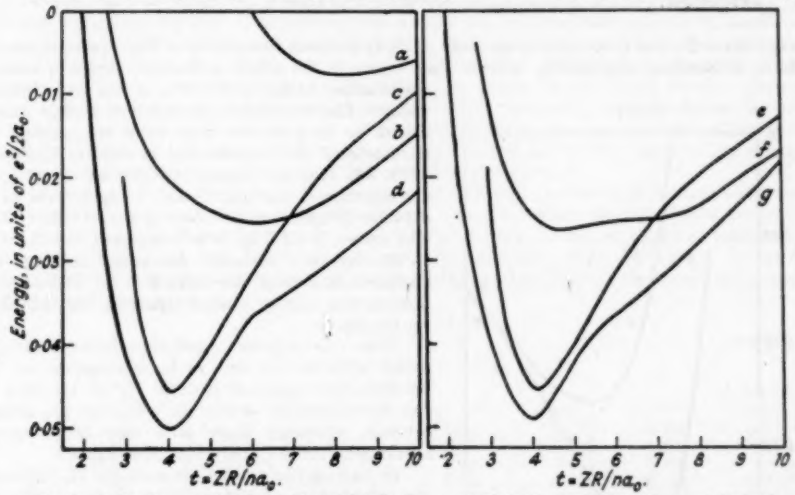
$$\phi_A^{sp^3} = \tfrac{1}{2}\phi_A^s \pm \frac{\sqrt{3}}{2}\phi_A^x \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (7)$$

Curve *A* results from use of the positive sign in (7), and curve *B* from that of the negative sign. Curve *C*, representing the best *s*–*p* admixture, is the same as curve *C* of Fig. 1.

Pauling and Sherman, using Slater 2*s* functions for ϕ_A^s, ϕ_B^s found that the sp^3-hybrid (positive sign) closely approximates the best bonding attainable from *s*–*p* mixing. This is not the case when the true ϕ_A^s, ϕ_B^s are used, for neither of the curves *A* and *B* of Fig. 2 corresponds to binding

FIG. 3. 3-*Quantum States of* H_2^+ [$H^+ + H$ (3s, 3p, 3d)].

FIG. 4. 3-*Quantum States of* H_2^+ [$H^+ + H$ (3s, 3p, 3d)].



a, 3s–3s. *b*, 3p–3p. *c*, 3d–3d. *d*, *Best* spd-*hybrid*. *e*, sd-*Hybrid*. *f*, sp-*Hybrid*. *g*, pd-*Hybrid*.

of comparable firmness to that shown in curve *C*; only at large internuclear separations does curve *A* begin to resemble curve *C*.

Excited States of H_2^+: 3-*Quantum States*.—In this section, the calculations are extended to the 3-quantum states of H_2^+, covering the bonding types *s*–*s*, *p*–*p*, *d*–*d*, and the hybrid admixtures *sp*-, *sd*-, *pd*-, and *spd*-. The eigenfunctions of the 3-quantum states of the H atom were used in the following form :

$$\phi_A^{3s} = \sqrt{\frac{\gamma^3}{\pi}} \cdot (1 - 2\gamma r_A + \tfrac{2}{3}\gamma^2 r_A^2)e^{-\gamma r_A} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (8)$$

$$\phi_A^{3p_z} = \sqrt{\frac{2\gamma^5}{3\pi}} \cdot r_A(2 - \gamma r_A)\cos\theta_A e^{-\gamma r_A} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (9)$$

$$\phi_A^{3d_z} = \sqrt{\frac{\gamma^7}{2\pi}} \cdot r_A^2(\cos^2\theta_A - \tfrac{1}{3})e^{-\gamma r_A} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (10)$$

$$\gamma = Z/3a_0 \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (11)$$

The calculated potential-energy curves ($Z = 1$) for the *s*–*s*, *p*–*p*, and *d*–*d* bonded states are shown in curves *a*, *b*, and *c* of Fig. 3. The curve *d* in this same figure represents the best bonding

attainable by *spd*-hybridization. The molecular constants of these states are summarized in Table II, and compared with the values calculated by Pauling and Sherman on the basis of the Slater approximations to equations (8), (9), and (10).

Curves representing the best hybrid states attainable from *sp*-, *sd*-, and *pd*-mixing are shown separately in Fig. 4.

The Ground-state of H_2^+: 1s-2p *Hybridization.*—It is well known that the binding in the ground state of the H_2^+ ion is not adequately described in terms of 1*s*–1*s* bonding. The potential-

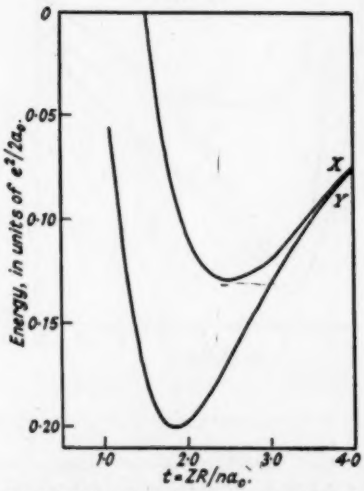
TABLE II.

Calculated constants in 3-quantum states of H_2^+.

Bonding.	D_e (this paper).	r_e	D_e (P. and S.).	r_e
3*s*–3*s*	0·00765	24·73	0·028	16·0
3*p*–3*p*	0·0254	18·52	0·074	10·5
3*d*–3*d*	0·0453	12·22	—	—
sp-Hybrid	0·0264	14·33	0·12	11·0
sd-Hybrid	0·0453	12·22	—	—
pd-Hybrid	0·0490	11·82	—	—
spd-Hybrid	0·0501	11·92	—	—

energy curve for the 1*s*–1*s* type of bonding ($Z = 1$) is shown in curve *X* of Fig. 5, and represents a form of bonding appreciably weaker than exists in the actual molecule. Curve *X* shows a dissociation energy only 63% of the experimental value. The calculated dissociation energy can be raised to 80% of the true value by varying the parameter *Z* (Finkelstein and Horwiotz, *Z. Physik*, 1928, **48**, 118) and raised still further to 97%, by simultaneously varying *Z* and using hybrid 1*s*–2*p* orbitals (Dickinson, *J. Chem. Phys.*, 1933, **1**, 317). The curve *Y* of Fig. 5 is calculated for the best 1*s*–2*p* hybrid, without, however, making any variation in *Z* from the value $Z = 1$. It leads to a dissociation energy almost equal to that obtained by Dickinson.

FIG. 5.



$H^+ + H(1s)$. *X*, 1s–1s. *Y* = 1s–2p-*Hybrid.*

These calculations suggest that the most effective *single* addition to the 1*s*–1*s* description of the bonding in the ground state of H_2^+ is attained by the hybridization of the 1*s* with the $2p_z$ atomic orbitals, although there is a very large energy separation (10·2 ev.) between these orbitals.

In case of the ground state of the H_2 molecule, the calculations of Rosen (*Phys. Review*, 1931, **38**, 2099) show that a mixing of 1*s* and $2p_z$ orbitals leads to a significant increase in the calculated energy, but here variation in the parameter *Z* is more effective *per se* than is the polarization of the 1*s*-orbitals. By simultaneous variation in *Z*, and mixing of 1*s*–$2p_z$ orbitals, Rosen arrived at a dissociation energy approaching 85% of the experimental value. It is interesting, however, that, at internuclear separations comparable with those near the equilibrium separation in H_2^+, Rosen finds that the effect of hybridization asserts itself as the dominant factor in raising the energy relative to that of the 1*s*–1*s* bonded molecule.

The very significant contribution of the $2p_z$ orbitals to the bonding in H_2^+, and the lesser but nevertheless important contribution in H_2, should be stressed. The relatively large energy separation of the 1*s* and 2*p* atomic orbitals of the H atom is seen to present a barrier insufficient to prevent an appreciable mixing of these orbitals when bond formation occurs. As a consequence, it is reasonable to expect that hybridization occurs more frequently than not, for in general the energy separations between neighbouring orbitals in atoms other than hydrogen are not larger than in the H atom itself.

Discussion.

From the data listed in Table I and II, it is apparent that use of Slater functions to describe excited states of H_2^+ (coupled with the approximations attached thereto) leads to results markedly different quantitatively from those of this paper. For example, if we confine attention to the *relative* strengths of different bond types, we find quite different ratios from those of Pauling and Sherman, *viz.*:

(a) 2-*Quantum states*, $ss : pp$: best sp-hybrid = 1 : 5·3 : 6·2, compared with 1 : 2·7 : 4·1 (Pauling).

(b) 3-*Quantum states*, $ss : pp$: best sp-hybrid = 1 : 3·3$_3$: 3·5, compared with 1 : 2·6$_4$: 4·0$_7$ (Pauling).

The differences in these ratios are more serious than in a purely quantitative sense, for, whereas Pauling and Sherman found an approximate *constancy* in the ratios of $ss : pp : sp^3$-hybrid in passing from the 2- to the 3-quantum states, our ratios do not show this type of behaviour. We hesitate to conclude that, in the general case, the strength of a hybrid bond stands neither in a simple nor in a constant ratio to the strengths of its parent bonds; but, on the other hand, it seems to us that the assumption of a simple 1 : 3 : 4 ratio for the ratio $ss : pp : sp^3$–sp^3 bond strengths has little real justification.

A further point of departure from Pauling and Sherman is seen in the comparison of the calculated bond lengths (r_e). The calculations of this paper show that the hybrid bonds are both stronger and shorter than their parents—*e.g.*, in the 2-quantum states r_e of the best hybrid is noticeably shorter than r_e of the s–s or p–p bonded states. Pauling and Sherman, on the contrary, found the r_e of the hybrids to lie in between the r_e of the parent bonds. Indeed, Pauling and Sherman concluded in their paper that "there is no simple inter-relation between bond-energy and internuclear distance." The calculations of this paper, whilst showing no very sharp dependence of dissociation energy on bond length, reveal that there exists a rough relationship in the sense that the shorter the bond, the stronger it is.

There are some interesting relations between the calculated r_e values and the force constants (k_e) of the various states of the H_2^+ molecule-ion. The k_e values were obtained by fitting Morse curves through three points calculated in the vicinity of the equilibrium position, as described by Rosen (*loc. cit.*) and Coulson (*Trans. Faraday Soc.*, 1937, **33**, 1485). These are given in Table III, together with the calculated r_e and D_e, expressed now in the more conventional units of A. and electron-volts.

Table III.

Calculated constants of H_2^+.

Bond.	r_e (A.).	D_e (ev.).	k_e (dynes × 10^5/cm.).	Bond.	r_e (A.).	D_e (ev.).	k_e (dynes × 10^5/cm.).
$1ss$	1·318	1·755	0·979	$1s2p$	0·979	2·706	2·152
$2ss$	5·67	0·2797	0·0172	$2s2p$	2·170	1·721	0·208
$3ss$	13·09	0·1035	0·00148	$3s3p$	7·583	0·358	0·0040
$2pp$	2·42	1·480	0·0943	$3p3d$	6·255	0·663	0·0197
$3pp$	9·80	0·343	0·00168	$3s3p3d$ ...	6·308	0·678	0·0161
$3dd$	6·467	0·613	0·0205	$^1\Sigma^+_g$ (obs.)	1·06	2·77	1·566

The relation of k_e to r_e is shown in the plot of $k^{-\frac{1}{3}}$ against r_e (Badger's rule) in Fig. 6. The straight lines in Fig. 6 are drawn through points corresponding to bonds of similar description—*e.g.*, curve *A* covers the $1ss$-, $2ss$-, and $3ss$-bonded states. Whilst it is perhaps incautious to draw conclusions from our limited data, Fig. 6 gives some ground for examining the Badger rule in series of similarly-bonded molecules—*e.g.*, the series of alkali-metal hydrides. This point is taken up more fully in the Appendix.

The present work was undertaken with the purpose of establishing more firmly Pauling and Sherman's semi-empirical relation between the strengths of hybrid and parent bonds. In this respect, the results obtained are disappointing, in that they suggest that hybrid bonding requires individual treatment in each specific case, and that simple generalizations are at best approximations. Some useful features that emerge from the present work may have a wider significance than in the particular and exceptional case of the H_2^+ molecule. For example, the considerable effect arising from the interaction of the states $1ss$ and $2pp$ in H_2^+ suggests that the simple description of many chemical bonds in terms of a single bond type—*e.g.*, s–s-, p–p-, s–p-bonds—may require revision in terms of hybrid descriptions. Recent experimental evidence (Townes and Dailey, *J. Chem. Physics*, 1949, **17**, 782) and some theoretical considerations by Moffitt (*Proc. Roy. Soc.*, 1950, *A*, **202**, 534) point in the same direction.

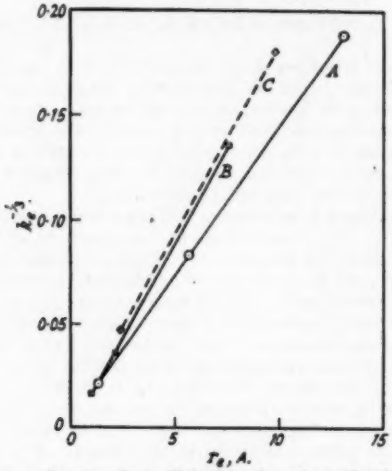
APPENDIX.

The empirical relation between force constant (k_e) and equilibrium bond length noticed by Badger (*J. Chem. Physics*, 1934, **2**, 128) is expressed by the equation:

$$k_e (r_e - d_{ij})^3 = C_{ij} \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (i)$$

FIG. 6.

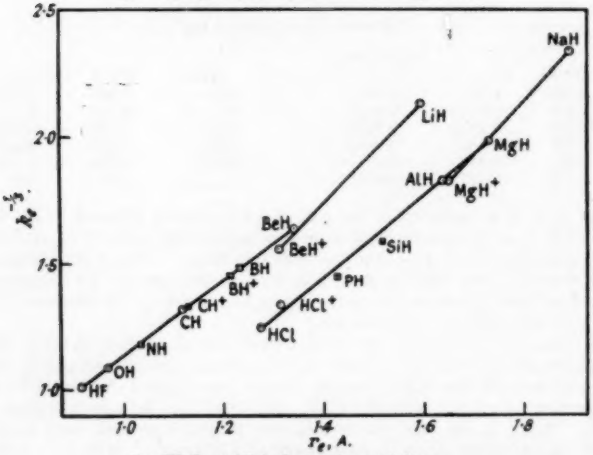
Badger's rule. Plot of $k_e^{-\frac{1}{3}}$ against r_e.



A, ss-*Bonds*. *B*, sp-*Hybrid bonds*. *C*, pp-*Bonds*.

FIG. 7.

Badger's rule for hydrides of 1st and 2nd period.



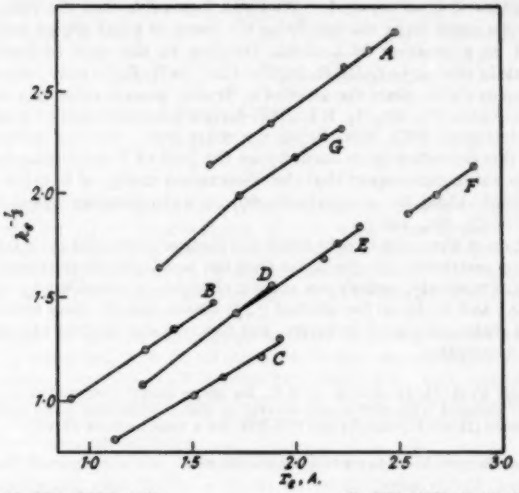
⊙ *Well-established experimental data.*
⊡ *Less-well-established experimental data.*

where d_{ij}, C_{ij} are constants characteristic of diatomic molecules made up from one element in the i-th row and one in the j-th row of the periodic table. In favourable cases—as, *e.g.*, in the ground states of the hydrides of the 1st- and 2nd-row elements (Fig. 7)—the Badger rule holds

good with an accuracy of the order 1%. In Fig. 7, separate lines have been drawn through the points HF ⟶ BeH, and BeH^+ ⟶ LiH (row 1), and similarly for the points HCl ⟶ MgH, MgH^+ ⟶ NaH (row 2), in order to discriminate between bonding which in first-order

FIG. 8.

Badger's rule applied to families.



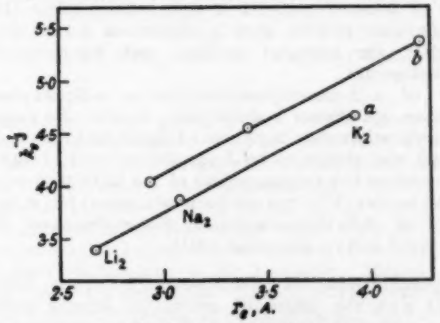
A, LiH, NaH, KH, RbH, CsH.
B, HF, HCl, HBr, HI.
C, CO, SiO, GeO, SnO, PbO.
D, BF, BCl, BBr.
E, BCl, AlCl, GaCl, InCl.
F, TlCl, TlBr, TlI.
G, BeH, MgH, CaH, SrH, BaH.

approximation may be described as *p*–*s* (HF ⟶ BeH; HCl ⟶ MgH), or as *s*–*s* (BeH^+ ⟶ LiH; MgH^+ ⟶ NaH).

It is not our purpose to examine Badger's rule in the form in which it was originally proposed, but rather to apply it to series of similarly-bonded molecules. Such a series is provided by the

FIG. 9.

Badger's rule for $^1\Sigma_g^+$ *and* $^1\Pi_u$ *states of* Li_2, Na_2, *and* K_2.



a, $^1\Sigma_g^+$ *States*. *b*, $^1\Pi_u$ *States*.

alkali-metal hydrides LiH, NaH, KH, RbH, CsH, in which the variation is in the principal quantum number of the valence electrons, comparing in this sense with the variation in passing from the 1*ss* ⟶ 2*ss* ⟶ 3*ss* states of H_2^+. Fig. 8 shows some examples of this mode of

application of Badger's rule. The examples shown do not exhaust the possibilities of the method, and several other families not shown give good linear plots—*e.g.*, [O_2, SO, S_2, Se_2, Te_2]; [CS, SiS, PbS]; [Cl_2, Br_2, I_2]; [P_2, PN, N_2].

Some significant deviations from linearity in a series may be caused by abrupt changes in bond character along a given series. For example, although the alkali-metal hydrides form a good linear family (curve *A*), the sub-group B hydrides (CuH, AgH, AuH) give a scattered set of points lying well removed from curve *A*. We think it possible that the difference between the A and the B sub-groups arises from the low-lying ^2D states of B sub-group metals (^2D in Cu; $3d^9$, $4s^2$) giving weight to a measure of *d*-orbital bonding in the case of CuH, AgH, and AuH. Similarly, the break in the curve *G* (BeH, MgH—CaH, SrH, BaH) may reflect the onset of some degree of *d*-bonding at CaH—since the atoms Ca, Sr, Ba, possess relatively low-lying ^3D states.

Although the halogens Cl_2, Br_2, I_2, ICl, ClBr, form a good example of a linear family, F_2 and F-containing interhalogens (FCl, FBr) lie off the main line. We can advance no good reason at the present for this deviation from linearity on the part of F-containing halogen compounds, but it may be significant in this respect that the dissociation energy of F_2 is low (Evans, Warhurst, and Whittle, *J.*, 1950, 1524) by comparison with an extrapolation based on the dissociation energies observed for Cl_2, Br_2, and I_2.

A neat illustration of the point that in making a Badger's rule plot for a family of compounds, the family should be restricted—in the sense that the bond character remains similar along the family series, or, alternatively, suffers no abrupt change—is provided by Fig. 9. This shows the plot for Li_2, Na_2, and K_2 in (*a*) the ground ($^1\Sigma_g^+$) states, and (*b*) the excited ($^1\Pi_u$) states. We note that identical states give good linearity, but the two sets of data are separate and require two lines for their description.

The authors thank Prof. M. G. Evans, F.R.S., for some useful discussions in connexion with this work, and Mr. J. S. Roberts who performed several of the calculations independently as a check on accuracy. One of them (H. O. P.) thanks the D.S.I.R. for a maintenance grant.

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213. *Reduction of Amides with Lithium Aluminium Hydride.*

By A. L. MORRISON, R. F. LONG, and (MISS) M. KÖNIGSTEIN.

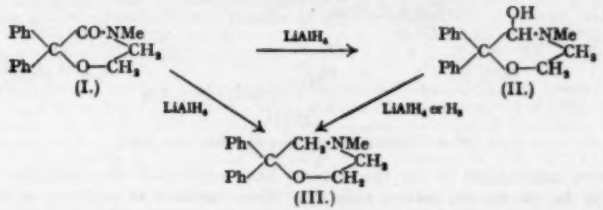
Reduction of 3-keto-4-methyl-2 : 2-diphenylmorpholine (I) with excess of lithium aluminium hydride gave a mixture of 4-methyl-2 : 2-diphenylmorpholine (III), the expected product, and 3-hydroxy-4-methyl-2 : 2-diphenylmorpholine (II).

Treatment of α-(2-dimethylaminoethoxy)-α : α-diphenylacetopiperidide (IV) with lithium aluminium hydride gave, besides the expected product 2-(2-dimethylaminoethoxy)-2 : 2-diphenyl-1-piperidinoethane (V), another substance which was shown to be 3-dimethylamino-1 : 1-diphenylpropanol (VII). The course of the rearrangement of the lithium aluminium hydride complex of (IV) to give (VII) has not been established but it has been shown that treatment of (2-diethylaminoethoxy)diphenylmethane ("Benadryl") (VI) with powdered sodium also gives (VII).

IT has recently been reported (Galinovsky and Weiser, *Experientia*, 1950, **6**, 377) that lactams, generally, when treated with the calculated amount of lithium aluminium hydride, yield amino-aldehydes, while excess of the reagent gives the oxygen-free amines.

It was reported by Morrison, Königstein, and Cohen (*J.*, 1950, 2887) that 3-keto-4-methyl-2 : 2-diphenylmorpholine (I) was formed by the action of thionyl chloride on sodium α-(2-dimethylaminoethoxy)-α : α-diphenylacetate. Reduction of (I) with excess of lithium aluminium hydride would be expected to yield 4-methyl-2 : 2-diphenylmorpholine (III) (Uffer

and Schlittler, *Helv. Chim. Acta*, 1948, **31**, 1397) which can be considered as a cyclic form of the well-known antihistaminic compound, " Benadryl," *i.e.* (2-diethylaminoethoxy)diphenylmethane. The product from the action of 2 moles of the hydride was found to be a mixture of (III) and 3-hydroxy-4-methyl-2 : 2-diphenylmorpholine (II).

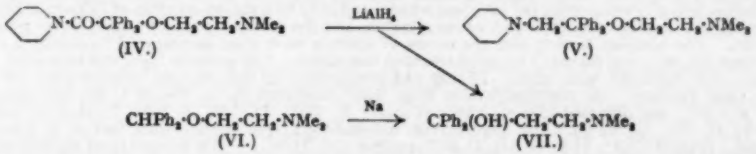


Catalytic hydrogenation of (II) gave (III), which was also formed in 88% yield by the further action of the hydride on (II). Condensation of (II) with nitromethane gave 4-methyl-3-nitromethyl-2 : 2-diphenylmorpholine, which on reduction with aluminium amalgam in moist ether yielded 3-aminomethyl-4-methyl-2 : 2-diphenylmorpholine. Hydrogenation of acetone in presence of the latter compound gave 4-methyl-2 : 2-diphenyl-3-*iso*propylaminomethylmorpholine.

The action of excess of lithium aluminium hydride on a number of amides structurally related to (I) was investigated, and in no case was there any evidence of formation of an aldehyde. The lactam, 1-methyl-3 : 3-diphenylpyrrolid-2-one, was reduced to 1-methyl-3 : 3-diphenylpyrrolidine. Open-chain amides such as the piperidides of diphenylacetic acid and benzilic acid were reduced to 1 : 1-diphenyl-2-piperidinoethane and 1-hydroxy-1 : 1-diphenyl-2-piperidinoethane, respectively.

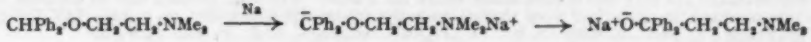
The reduction of the piperidide of α-(2-dimethylaminoethoxy)-α : α-diphenylacetic acid (IV) was then investigated, the products to be expected being either 2-(2-dimethylaminoethoxy)-2 : 2-diphenyl-1-piperidinoethane (V) or α-(2-dimethylaminoethoxy)-α : α-diphenylacetaldehyde. Treatment of (IV) with 1 mole of the hydride gave (V) (30% yield) and 3-dimethylamino-1 : 1-diphenylpropan-1-ol (32% yield), the latter being identified with the compound investigated by Morrison and Rinderknecht (*J.*, 1950, 1510).

It has also been observed that on heating a solution of (2-dimethylaminoethoxy)diphenylmethane (VI) in benzene with powdered sodium, the solution underwent a series of colour changes through blue, green, and yellow, finally becoming brown when cooled, and gave, as

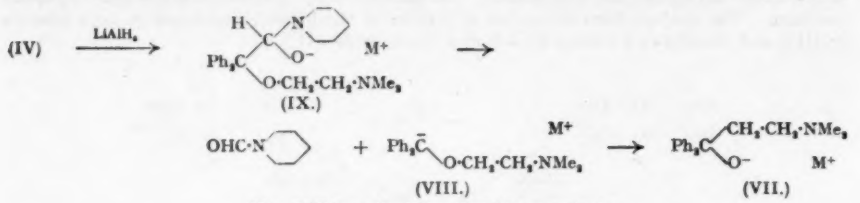


the only identified product, (VII) in at least 30% yield. This change from (VI) to (VII) is in accordance with the work of Schorigin (*Ber.*, 1923, **56**, 176; 1924, **57**, 1627, 1634; 1925, **58**, 2028; 1926, **59**, 2510) who showed that certain ethers when heated with sodium underwent, apart from a splitting of the molecule, a " carbinol rearrangement " to give an alcohol. We have not studied this reaction extensively but it would appear from the complete absence of any colour change that diphenylmethyl 3-piperidinopropyl ether is unaffected when heated with powdered sodium in toluene, indicating that the fission of the ether in the required manner is dependent on the tertiary amino-group in the β-position. Moreover, in conformity with Schorigin's observations, we have established that 2-dimethylaminoethyl diphenylmethyl thioether does not give a thiol corresponding to (VII), although there is evidence of the fission of the thioether.

If we formulate the reaction of sodium with (VI) as follows :



we can regard the reaction of lithium aluminium hydride with (IV) as taking the following course:



(M = Lithium aluminium hydride complex.)

In the above mechanism of the reaction we have essentially the reductive cleavage of a C–C bond. As far as we are aware, only one other instance of such an action by lithium aluminium hydride has been reported, namely, the formation of 4-ketoquinolizidine from 3-carbethoxy-4-ketoquinolizidine (Boekelheide and Rothchild, *J. Amer. Chem. Soc.*, 1949, **71**, 879).

It might be argued that the rearrangement of (VIII) to (VII) was very unlikely under the mild conditions employed, but it has been shown by Ziegler and Thielmann (*Ber.*, 1923, **56**, 1741) that diphenylmethyl ethyl ether in ethereal solution is split by the action of potassium at room temperature into diphenylmethylpotassium and phenol. The only other product isolated from our reaction mixture was a very small amount of a base which gave a reineckate the m. p. of which was not depressed when mixed with piperidine reineckate. Further work will be necessary to determine definitely if piperidine is formed and also whether formaldehyde or formic acid is the other product of the reaction.

None of the new compounds described in this paper has been found to possess outstanding spasmolytic properties.

Experimental.

1-Methyl-3 : 3-diphenylpyrrolidine.—1-Methyl-3 : 3-diphenylpyrrolid-2-one (1·6 g.) in dry ether (20 ml.) was added to a stirred solution of lithium aluminium hydride (0·4 g.) in ether (30 ml.) in an atmosphere of nitrogen. The mixture was refluxed for 20 hours, and the cooled product decomposed by gradual addition of water, and then made acid with 2N-sulphuric acid. The acid layer was separated and made alkaline with 30% sodium hydroxide solution, the base taken up in ether, and the ethereal solution dried and concentrated. The residual oil (0·7 g.) on distillation gave the pure *pyrrolidine*, b. p. 140—142°/1 mm. (Found: C, 85·6; H, 8·3; N, 6·0. $C_{17}H_{19}N$ requires C, 86·1; H, 8·0; N, 5·9%). The *picrate*, recrystallised from alcohol, had m. p. 162—163° (Found: C, 59·3; H, 4·9; N, 12·3. $C_{23}H_{22}O_7N_4$ requires C, 59·2; H, 4·7; N, 12·0%).

3-Hydroxy-4-methyl-2 : 2-diphenylmorpholine (II).—A solution of 3-keto-4-methyl-2 : 2-diphenylmorpholine (5·9 g.) in dry ether (50 ml.) was added gradually to a stirred solution of lithium aluminium hydride (1·6 g.) in dry ether (200 ml.) under nitrogen, and the reaction mixture heated under reflux for 24 hours. The complex formed and the excess of hydride were then decomposed by addition of ice-cold water (30 ml.), and excess of 5N-sulphuric acid was added. The aqueous layer was separated, made alkaline, and extracted with ether. Drying and evaporation of the ethereal solution gave 5·0 g. of crude basic product. On recrystallisation from light petroleum (b. p. 60—80°), the *carbinolamine*, m. p. 97—99°, was obtained (1·9 g., 32%) (Found: C, 75·8; H, 6·8; N, 5·2. $C_{17}H_{19}O_2N$ requires C, 75·4; H, 7·1; N, 5·2%). The *hydrochloride* recrystallised from alcohol–ether had m. p. 194—195° (decomp.) (Found: Cl^-, 11·8. $C_{17}H_{20}O_2NCl$ requires Cl^-, 11·6%). The *picrate*, from alcohol, melted at 164—165° (Found: N, 11·6. $C_{23}H_{22}O_9N_4$ requires N, 11·25%).

4-Methyl-2 : 2-diphenylmorpholine (III).—(*a*) The light petroleum mother-liquors from recrystallisation of the above carbinolamine gave on concentration the *morpholine*, which was purified (m. p. 79—80°; 2·2 g., 39%) by recrystallisation from a small amount of light petroleum (b. p. 60—80°) (Found: C, 80·2; H, 7·6; N, 5·2. $C_{17}H_{19}ON$ requires C, 80·6; H, 7·5; N, 5·5%).

(*b*) 3-Hydroxy-4-methyl-2 : 2-diphenylmorpholine (2 g.), dissolved in ethanol, was hydrogenated by means of a 5% palladium–charcoal catalyst (0·3 g.), the theoretical amount of hydrogen being taken up in 5 hours. The residue remaining after distillation of the alcohol distilled at 140—150°/0·5 mm., and the solid distillate recrystallised from light petroleum (b. p. 40—60°) to give the pure morpholine, m. p. 79—80°. The *hydrochloride* melted at 266—268° (decomp.) (Found: C, 69·9; H, 6·8; N, 4·7; Cl^-, 12·8. $C_{17}H_{20}ONCl$ requires C, 70·3; H, 6·9; N, 4·8; Cl^-, 12·3%). The *picrate* melted at 233—234° (Found: N, 11·6. $C_{23}H_{21}O_9N_4$ requires N, 11·6%).

(*c*) Reaction of (II) (2 g.) in dry ether (30 ml.) with lithium aluminium hydride (0·3 g.) in dry ether (50 ml.) under nitrogen for 14 hours yielded (III) in 88% yield.

4-Methyl-3-nitromethyl-2 : 2-diphenylmorpholine.—A solution of the above carbinolamine (5·0 g.) in nitromethane (20 ml.) was heated under reflux for 1 hour. The solid product left on distilling off the nitromethane, recrystallised from alcohol, gave the *nitromethyl-morpholine*, m. p. 144—145° (5·3 g., 92%) (Found: C, 68·8; H, 6·45; N, 9·1. $C_{18}H_{20}O_3N_2$ requires C, 69·2; H, 6·4; N, 8·9%).

3-Aminomethyl-4-methyl-2 : 2-diphenylmorpholine.—A solution of the above nitromethylmorpholine (2 g.) in moist ether (150 ml.) was allowed to react with aluminium amalgam (prepared from foil, 2·5 g.) for 12 hours. The filtered ethereal solution was dried and concentrated to give a viscous oil, b. p. 156—160°/0·2 mm. The *dihydrochloride* melted at 200—203° (63%) (Found : C, 58·1; H, 7·2; N, 7·85; Cl^-, 18·9. $C_{18}H_{24}ON_2Cl_2$ requires C, 57·7; H, 6·75; N, 7·9; Cl^-, 20·0%).

4-Methyl-2 : 2-diphenyl-3-isopropylaminomethylmorpholine.—Hydrogenation of acetone (1 ml.) in presence of the above aminomethylmorpholine (2 g.) in ethanol (50 ml.) with reduced platinum oxide (0·1 g.) yielded the *iso*propylamine as an oil, b. p. 180—184°/0·3 mm. (68%). The *dihydrochloride* had m. p. 242—244° (decomp.) (Found : C, 63·4; H, 8·1; N, 7·4; Cl^-, 17·2. $C_{21}H_{30}ON_2Cl_2$ requires C, 63·5; H, 7·6; N, 7·1; Cl^-, 17·8%).

1 : 1-Diphenyl-2-piperidinoethane.—*Diphenylacetopiperidide* was prepared from diphenylacetyl chloride (1·5 g.) and piperidine (1·1 g.) in dry ether and obtained as a crystalline solid, m. p. 107—108°, from light petroleum (b. p. 60—80°) (Found : N, 5·0. $C_{19}H_{21}ON$ requires N, 5·0%). This piperidide (1·3 g.) was reduced with lithium aluminium hydride (0·2 g.) to give the base as an oil which was converted into the *hydrochloride*, m. p. 145—147° (0·95 g., 65%) (Found : N, 4·6; Cl^-, 11·05. $C_{19}H_{24}NCl$ requires N, 4·3; Cl^-, 11·7%).

1-Hydroxy-1 : 1-diphenyl-2-piperidinoethane.—By the action of phenylmagnesium bromide [from bromobenzene (20 g.) and magnesium (3·1 g.)] on 1-ethoxalylpiperidine (6 g.) in ethereal solution, *α-hydroxy-α : α-diphenylacetopiperidide* was obtained as a crystalline solid (68%), m. p. 121—122°, from light petroleum (b. p. 60—80°) (Found : N, 4·2. $C_{19}H_{21}O_2N$ requires N, 4·75%). This piperidide (3·0 g.) was treated with lithium aluminium hydride (0·45 g.) as described above. On decomposition of the lithium aluminium complex with dilute sulphuric acid, *1-hydroxy-1 : 1-diphenyl-2-piperidinoethane hydrogen sulphate* (54·5%, 2·1 g.) separated; recrystallised from alcohol–ether, it had m. p. 165—166° (Found : N, 3·7; S, 8·9. $C_{19}H_{23}O_5NS$ requires N, 3·7; S, 8·4%). On working up of the filtrate from this sulphate in the usual way, the *base* was isolated in 21% yield (0·6 g.) as a solid, m. p. 65—66°, from benzene–light petroleum (b. p. 40—60°) (Found : N, 5·0. $C_{19}H_{23}ON$ requires N, 5·0%).

Reaction of Lithium Aluminium Hydride with α-(2-Dimethylaminoethoxy)-α : α-diphenylacetopiperidide.—The piperidide (4·5 g.) was allowed to react with lithium aluminium hydride (0·75 g.) in ether (120 ml.) for 16 hours. The basic product was isolated in the usual manner and found to be easily separated into two substances, one soluble and the other insoluble in light petroleum (b. p. 40—60°). The former was purified *via* its picrate, m. p. 180°, which was decomposed with a solution of lithium hydroxide. The regenerated base in ether was treated with an alcoholic solution of hydrogen chloride to give solvated *2-(2-dimethylaminoethoxy)-2 : 2-diphenyl-1-piperidinoethane hydrochloride*, m. p. 221—222° (28%) (Found : C, 63·1; H, 8·3; N, 6·1; Cl^-, 15·5. $C_{23}H_{34}ON_2Cl_2.C_2H_4O$ requires C, 63·7; H, 8·5; N, 5·9; Cl^-, 15·1%).

The substance insoluble in the light petroleum was recrystallised from light petroleum (b. p. 60—80°) and had m. p. 163—164°, not depressed when mixed with an authentic specimen of 3-dimethylamino-1 : 1-diphenylpropan-1-ol, m. p. 164—165° [Found : C, 79·8; H, 8·85; N, 5·7%; *M* (Rast), 230. Calc. for $C_{17}H_{21}ON$: C, 80·0; H, 8·2; N, 5·7%; *M*, 255]. The identity of the substance was further established (cf. Morrison and Rinderknecht, *loc. cit.*) by preparation and mixed m. p. determinations of the hydrochloride, m. p. 204—205° (Found : C, 69·2; H, 7·2; N, 4·7; Cl^-, 11·8. Calc. for $C_{17}H_{22}ONCl$: C, 70·0; H, 7·55; N, 4·7; Cl^-, 12·2%), and of the *picrate*, m. p. 151—152° (Found : N, 11·7. $C_{23}H_{24}O_8N_4$ requires N, 11·3%).

The alkaline aqueous phase, after the normal ether-extraction of these two basic products, was distilled into dilute hydrochloric acid, and this acid solution concentrated to dryness. The hydrochloride left (0·4 g.) was converted into the reineckate, which melted at 256—257° undepressed when mixed with *piperidine reinechate*, m. p. 258—259° (Found : C, 26·8; H, 4·3; N, 23·8. $C_2H_{11}N_7S_4Cr$ requires C, 26·8; H, 4·2; N, 24·2%).

Action of Sodium on (VI).—A solution of (VI) (4 g.) in toluene (100 ml.) was heated under reflux with powdered sodium (0·4 g.) in an atmosphere of nitrogen with stirring for 8 hours, the solution undergoing the colour changes described on p. 953. On working up of the reaction mixture in the usual way for basic material, a solid, m. p. 164—165°, was isolated in 30% yield and was shown by mixed m. p. determination to be (VII) (Found : C, 80·05; H, 8·5. Calc. for $C_{17}H_{21}ON$: C, 80·0; H, 8·2%). The hydrochloride melted at 204—205° undepressed when mixed with an authentic specimen of the hydrochloride of (VII). The quaternary salt prepared from a benzene solution of the above carbinol and allyl bromide was shown to be identical with *allyldimethyl-(3 : 3-diphenyl-3-hydroxypropyl)ammonium bromide*, m. p. 229°, prepared from (VII) (Found : C, 63·9; H, 7·0; N, 3·7; Br^-, 21·2. $C_{20}H_{26}ONBr$ requires C, 63·8; H, 6·9; N, 3·7; Br^-, 21·7%).

Action of Sodium on 2-Dimethylaminoethyl Diphenylmethyl Sulphide.—The sulphide was prepared as described in Example I of U.S.P. 2,483,671. A solution of it (7·0 g.) in toluene (50 ml.) was added with stirring to powdered sodium (0·65 g.) in toluene (75 ml.) in an atmosphere of nitrogen. The mixture was gradually heated to boiling, and a red colour slowly developed, becoming a deep vivid crimson after 30 minutes. Heating was continued for a further two hours. The toluene solution was then cooled and carefully treated with water, and the aqueous extract treated with excess of mercuric chloride solution. Decomposition of the mercury salt (8·6 g.) by suspension in 20% hydrochloric acid (50 ml.) and passage of hydrogen sulphide, filtration from mercuric sulphide, and concentration of the mother-liquor gave a small amount (0·6 g.) of a very deliquescent, white, crystalline solid, m. p. 144—147°, which from analysis and properties would appear to be essentially 2-dimethylaminoethanethiol hydrochloride (Found : N, 9·4; S, 20·1. Calc. for $C_4H_{12}NSCl$: N, 9·9; S, 22·6%). From the toluene solution 2·3 g. of the hydrochloride of the sulphide were recovered.

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[*Received, January 11th*, 1951.]

214. *Unsaturated Lactones. Part II. Phenolic Butenolides related to "Hexœstrol" and "Stilbœstrol."*

By N. R. Campbell and J. H. Hunt.

Phenolic butenolides analogous to the synthetic œstrogens, 3 : 4-di-(*p*-hydroxyphenyl)-*n*-hexane (hexœstrol) and 3 : 4-di-(*p*-hydroxyphenyl)-*n*-hex-3-ene (stilbœstrol), have been prepared.

Since the discovery of the potent synthetic œstrogens now known as hexœstrol (Campbell, Dodds, and Lawson, *Nature*, 1938, **142**, 1121), stilbœstrol (Dodds, Golberg, Lawson, and Robinson, *Proc. Roy. Soc.*, 1939, *B*, **127**, 140), and dienœstrol (Dodds *et al.*, *loc. cit.*), the not unreasonable assumption has been made from time to time that the structural similarity between this type of œstrogen and œstradiol, noted by Dodds *et al.* (*loc. cit.*), might be paralleled in compounds having a similar diphenylhexane nucleus, but bearing groups characteristic of pharmacologically active steroids of other types.

Jaeger and Robinson (*J.*, 1941, 1744) prepared 3-(*p*-acetylphenyl)-4-(*p*-hydroxyphenyl)hex-3-ene, but this lacked progestational activity, probably because the phenolic hydroxyl group conferred œstrogenic activity on the compound. Linnell and Roushdi (*Quart. J. Pharm. Pharmacol.*, 1941, **14**, 270) reported that 3-(*p*-hydroxyphenyl)-4-(*m*-hydroxyacetylphenyl)hex-3-ene had rather less than one two-hundredth of the activity of deoxycorticosterone in prolonging the life of the young adrenalectomised rat. Corticosterone-like activity has been claimed for 3-(*p*-hydroxyacetylphenyl)- and 3-(*p*-acetoxyacetylphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane (Wellcome Foundation Ltd., Brownlee, and Duffin, B.P. 550,262).

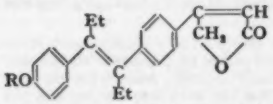
More recently, Biggerstaff and Wilds (*J. Amer. Chem. Soc.*, 1949, **71**, 2132) have prepared 3-(*p*-acetylphenyl)-4-(*p*-hydroxyphenyl)- and 3-(*p*-acetoxyacetylphenyl)-4-(*p*-acetoxyphenyl)-*n*-hex-3-ene, and also the corresponding hexanes. Their work is particularly interesting since they established the configuration of their products.

When the present work was started (1945), no extension of this principle had been made to include possible cardioactive substances bearing the butenolide or α-pyrone rings characteristic of the two main classes of cardiac aglycones. Elderfield and his collaborators (*J. Org. Chem.*, 1941, **6**, 260, 566, 577; 1942, **7**, 362, 444; 1943, **8**, 37, 129, 167; *J. Pharmacol.*, 1942, **74**, 381; 1943, **76**, 31; **77**, 401) had carried out some preliminary work on simple, substituted butenolides and α-pyrones and had found indications of cardioactivity in certain esters of coumalic acid and in a β-naphthyl butenolide. Part I of the present series (Campbell and Hunt, *J.*, 1947, 1176) was concerned with esters of coumalic and aconic acids.

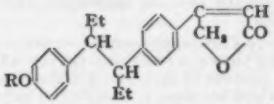
It was evidently desirable to prepare analogues of hexœstrol and stilbœstrol, in which one of the phenolic hydroxyl groups was replaced by the butenolide ring, thereby obtaining compounds which would bear some superficial resemblance to digitoxigenin. Linnell and Said (*J. Pharm. Pharmacol.*, 1949, **1**, 151) have claimed the preparation of 3-(*p*-2 : 5-dihydro-5-keto-3-furylphenyl)-4-(*p*-methoxyphenyl)-*n*-hex-3-ene (I), described as a pale yellow substance, m. p. 94—95°, which they were unable to demethylate.

The method used for the preparation of butenolides from acetoxymethyl ketones in all experiments to be described was that employed by Linville and Elderfield (*J. Org. Chem.*, 1941, **6**, 270). Using this method, we have carried out a Reformatsky reaction, with ethyl bromoacetate, on the *trans*-3-(*p*-acetoxyacetylphenyl)-4-(*p*-acetoxyphenyl)-*n*-hex-3-ene of Biggerstaff and Wilds (*loc. cit.*) and, by treating the crude reaction product with a mixture of hydrochloric and acetic acids, have obtained therefrom the phenolic butenolide (II). This butenolide was methylated; the product, a white solid, melted at 164° and was evidently quite distinct from Linnell and Said's product. In order to investigate this discrepancy, an acetoxymethyl ketone was prepared from *trans*-3-(*p*-carboxyphenyl)-4-(*p*-methoxyphenyl)-*n*-hex-3-ene (Neher and Miescher, *Helv. Chim. Acta*, 1946, **29**, 449; see also Biggerstaff and Wilds, *loc. cit.*), through the diazo-ketone. This acetoxymethyl ketone was a solid, m. p. 94°, whereas the ketone obtained by Linnell and Said was an oil, having a far from satisfactory analysis (*loc. cit.*). The solid ketone was converted into the corresponding butenolide by the Elderfield–Reformatsky process, the product melting at 164° and showing no depression of m. p. on admixture with the methoxy-butenolide obtained as above by methylation of the phenolic butenolide. On the evidence available, we are unable to account for this most notable difference between our acetoxymethyl ketone and butenolide and Linnell and Said's corresponding products.

3-(*p*-Methoxyphenyl)-4-phenyl-*n*-hexane has been described by Brownlee, Copp, Duffin, and Tonkin (*Biochem. J.*, 1943, **37**, 575); this substance was subjected, by Brownlee and Duffin (*loc. cit.*), to a Friedel–Crafts reaction with chloroacetyl chloride, yielding a substance, m. p. 139—141°, assumed to be 3-(*p*-chloroacetylphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane. An example in the same patent specification refers to the corresponding 3-(*p*-acetoxyacetylphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane, but no physical characteristics are given. We have carried out an acetolysis of the chloro-ketone and have obtained an acetoxymethyl ketone melting at 99°. That this ketone had arisen by chloroacetylation in the *p*-position of the unsubstituted phenyl nucleus was demonstrated by comparison with a specimen prepared from 3-(*p*-carboxyphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane, by reaction of its acid chloride with diazomethane and acetolysis of the diazomethyl ketone formed. The two specimens were identical, having m. p. and mixed m. p. 99°; the ultimate analysis was also satisfactory.



(I; R = Me.) (II; R = H.)



(III; R = Me.) (IV; R = H.)

The 3-(*p*-carboxyphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane above was first prepared in this investigation from the *p*-acetylphenylhex-3-ene prepared by Jaeger and Robinson (*loc. cit.*) from the corresponding 4-cyano-compound. The ketone, which was oily and presumably a mixture of the *cis*- and *trans*-isomers, was hydrogenated, by aid of palladium-black. The crude product partly crystallised and was recrystallised to give the saturated ketone, m. p. 134°. This ketone was then oxidised with sodium hypobromite to the methoxy-acid. Demethylation of a small quantity of this acid with a solution of hydrogen bromide in acetic acid gave 3-(*p*-carboxyphenyl)-4-(*p*-hydroxyphenyl)-*n*-hexane, m. p. 166°. Biggerstaff and Wilds (*loc. cit.*) have since described both acids, which they have prepared from Jaeger and Robinson's 3-(*p*-cyanophenyl)-4-(*p*-methoxyphenyl)hex-3-ene by a different route. They have, moreover, shown by degradation that the acids have the same configuration about the central carbon atoms as that existing in hexœstrol (*meso*). The structure of the acetoxymethyl ketone is thus completely defined.

On subjecting this ketone to a Reformatsky reaction with ethyl bromoacetate, a crude product was obtained, which, after being heated with a mixture of hydrochloric and acetic acids, yielded the methoxy-butenolide (III), 3-(*p*-2 : 5-dihydro-5-keto-3-furylphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane, m. p. 200°. Treatment of the crude Reformatsky product under more vigorous conditions, with hydrogen bromide in acetic acid, caused demethylation, in addition to lactonisation, yielding the hydroxy-butenolide, 4-(*p*-2 : 5-dihydro-5-keto-3-furylphenyl)-3-(*p*-hydroxyphenyl)-*n*-hexane (IV), m. p. 136°. This phenolic butenolide was also obtained by demethylation of the above methoxy-butenolide (III) with a solution of hydrogen bromide in acetic acid.

The phenolic butenolide (IV) was also prepared by the same procedure, 3-(*p*-acetoxyacetylphenyl)-4-(*p*-acetoxyphenyl)-*n*-hexane (Biggerstaff and Wilds, *loc. cit.*) being used in the Reformatsky reaction.

The four new butenolides all gave strong positive reactions in the Légal test; they have been submitted for pharmacological investigation.

Experimental.

The zinc powder used in Reformatsky reactions was prepared from a commercial grade by washing with 5% hydrobromic acid, followed by water several times, then alcohol, acetone, and finally ether. The product was dried in high vacuum over a Bunsen flame. In each case, the Reformatsky reaction was initiated by addition of a crystal of iodine. The benzene used was dried over sodium.

4-(p-2 : 5-*Dihydro*-5-*keto*-3-*furylphenyl*)-3-(p-*hydroxyphenyl*)-*n*-*hex*-3-*ene* (II).—A mixture of zinc powder (3·2 g.) and 4-(*p*-acetoxyacetylphenyl)-3-(*p*-acetoxyphenyl)-*n*-hex-3-ene (3·4 g.) (Biggerstaff and Wilds, *loc. cit.*) was covered with dry benzene (60 ml.), of which 30 ml. were then distilled off. Ethyl bromoacetate (3·5 g.) in dry benzene (5 ml.) was then added to the refluxing mixture in four portions, with constant stirring, during 15 minutes. The reaction commenced almost immediately and continued gently for 20 minutes, in an oil-bath at 100°. The bath-temperature was then raised to 120°, and the heating of the stirred mixture continued for 30 minutes. After cooling, alcohol (2 ml.) was added, followed by 10% hydrochloric acid (30 ml.) and a little ether to assist in dispersing the zinc complex. After removal of the zinc by filtration, the benzene solution was separated, washed twice with water, and dried ($MgSO_4$). Removal of the solvent left a gummy, yellow product (5·6 g.), a portion

of which (4·2 g.) was heated with stirring under reflux with concentrated hydrochloric acid (50 ml.), in an atmosphere of nitrogen for 90 minutes. The cooled mixture was then poured into ice-water and extracted with ether. The ether extract was washed thoroughly with sodium hydrogen carbonate solution and passed through a short column of alumina (Spence, standard). After elution with more ether, the solvent was evaporated, and the solid residue recrystallised from a little benzene. The *butenolide* (II) was a pale yellow, microcrystalline powder (0·82 g.), m. p. 165°, raised to 171—172° by further recrystallisation (charcoal) from methyl acetate–*cyclo*hexane (Found: C, 79·0; H, 6·6. $C_{23}H_{22}O_3$ requires C, 79·0; H, 6·65%).

4-(p-2 : 5-*Dihydro*-5-*keto*-3-*furylphenyl*)-3-(p-*methoxyphenyl*)-n-*hex*-3-*ene* (I).—(*a*) The foregoing phenolic butenolide (50 mg.), dissolved in dioxan (1 ml.), was shaken for 1 hour with methyl sulphate (20 mg.), with gradual addition of 0·5N-sodium hydroxide solution (0·33 ml.), causing separation of solid material. Water was added, and the product extracted with a little benzene. Addition of light petroleum (b. p. 40—60°) induced the separation of a small amount of sticky material which was rejected. On evaporation of the solution, the residue (20 mg.) crystallised, and was recrystallised from methyl acetate–light petroleum (b. p. 40—60°), giving the *butenolide* (I) in colourless plates, m. p. 164° (mixed m. p. with the phenolic butenolide, 139—144°) (Found: C, 78·8; H, 6·7. $C_{23}H_{24}O_3$ requires C, 79·3; H, 6·9%).

(*b*) 4-(*p*-Carboxyphenyl)-3-(*p*-methoxyphenyl)-*n*-hex-3-ene (m. p. 176°) (Neher and Miescher, *loc. cit.*) (2·8 g.) was converted into the acid chloride by heating under reflux for 2 hours with benzene (15 ml.), thionyl chloride (2 ml.), and 2 drops of pyridine. The crude acid chloride, freed from excess of thionyl chloride and benzene, crystallised in pale yellow rosettes. Ether (20 ml.) was added, and the solution decanted from pyridine hydrochloride and added slowly, with stirring, to an ethereal solution of diazomethane prepared from nitrosomethylurea (10 g.) (Arndt and Amende, *Z. angew. Chem.*, 1931, **43**, 444), kept below 5°. The mixture was set aside overnight, and the ether evaporated under reduced pressure, leaving 4-(p-*diazoacetylphenyl*)-3-(p-*methoxyphenyl*)-n-*hex*-3-*ene* as a yellow solid. A portion, recrystallised from benzene–light petroleum, had m. p. 136—137° (Found: N, 8·5. $C_{21}H_{22}O_2N_2$ requires N, 8·4%). The diazoketone was added in portions to boiling acetic acid (30 ml.) during 10 minutes and the yellow solution was then heated under reflux for a further 30 minutes. The mixture was cooled and poured into water, and the gummy product extracted with ether. The ethereal solution was washed with water and with sodium hydrogen carbonate solution and dried ($MgSO_4$), and the ether removed. The residue crystallised, and was twice recrystallised from acetone–light petroleum, yielding 4-(p-*acetoxyacetylphenyl*)-3-(p-*methoxyphenyl*)-n-*hex*-3-*ene* (1·7 g.), m. p. 96° (Found: C, 74·9; H, 7·2. $C_{23}H_{26}O_4$ requires C, 75·4; H, 7·1%). This ketone (1·5 g.) was dissolved in dry benzene (20 ml.), zinc powder (1·45 g.) was added, and the mixture heated to boiling. A solution of ethyl bromoacetate (2·25 ml.) in benzene (10 ml.) was then added dropwise. The reaction proceeded smoothly and the mixture was heated under reflux for 1 hour. After cooling, the mixture was treated with dilute sulphuric acid in the usual manner; evaporation of the separated and washed benzene solution left a gum, which was heated under reflux, in an atmosphere of nitrogen, with a mixture of concentrated hydrochloric acid (20 ml.) and acetic acid (5 ml.), with stirring for 1 hour. An equal quantity of the hydrochloric–acetic acid mixture was then added, and the mixture heated under reflux for a further hour. After cooling, the product was extracted with benzene, and the extract washed with sodium hydrogen carbonate solution. The dried benzene solution was passed through a column of alumina, which was then eluted with more benzene. Evaporation of the benzene eluates yielded a crystalline residue (0·4 g.) which was twice recrystallised from benzene–*cyclo*hexane, giving the product in colourless plates, m. p. 163—164°, not depressed on admixture with the material obtained as in (*a*) (Found: C, 79·0; H, 7·0%).

3-(p-*Acetylphenyl*)-4-(p-*methoxyphenyl*)-n-*hexane*.—3-(*p*-Acetylphenyl)-4-(*p*-methoxyphenyl)-*n*-hex-3-ene (Jaeger and Robinson, *loc. cit.*) (1·76 g.), dissolved in acetone (20 ml.), was shaken in hydrogen with palladium black (0·2 g.). The theoretical volume of hydrogen was absorbed in 3½ hours. After removal of catalyst, the acetone was distilled off, leaving an oily product which partly crystallised when kept. The crystalline material, collected and washed with methanol, had m. p. 110—120°, raised to 134° on recrystallisation from methanol (Biggerstaff and Wilds, *loc. cit.*, give m. p. 135—137° for this substance) (Found: C, 81·0; H, 8·4. Calc. for $C_{21}H_{26}O_2$: C, 81·2; H, 8·4%). Its 2 : 4-dinitrophenylhydrazone had m. p. 177°, and its semicarbazone, m. p. 221°.

3-(p-*Carboxyphenyl*)-4-(p-*methoxyphenyl*)-n-*hexane*.—The above ketone (1·5 g.) was shaken for 5 hours with a mixture of dioxan (5 ml.) and sodium hypobromite solution (from bromine, 1 ml.; sodium hydroxide, 1·76 g.; and ice-water, 10 ml.). Next morning, the slight excess of hypobromite was removed by sodium pyrosulphite solution. The insoluble sodium salt was collected, washed with water, and decomposed by warming it for 15 minutes with dilute sulphuric acid. The crude product was collected and dried (1·38 g., 91%); after recrystallisation from *cyclo*hexane the m. p. was 166—168° (corr. 169·5—171·5°), not depressed on admixture with a specimen of the acid prepared by the method of Biggerstaff and Wilds (*loc. cit.*) (Found: C, 77·2; H, 8·0. Calc. for $C_{20}H_{24}O_3$: C, 76·9; H, 7·7%).

Demethylation. The above methoxy-acid (200 mg.) was heated under reflux for 2 hours with a 50% solution of hydrogen bromide in acetic acid, then cooled and poured into water. The collected solid, recrystallised three times from benzene–*cyclo*hexane had m. p. 166°, not depressed on admixture with a specimen of 3-(*p*-carboxyphenyl)-4-(*p*-hydroxyphenyl)-*n*-hexane prepared by the method of Biggerstaff and Wilds (*loc. cit.*).

3-(p-*Acetoxyacetylphenyl*)-4-(p-*methoxyphenyl*)-n-*hexane*.—(*a*) 3-(*p*-Carboxyphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane (1 g.) was heated under reflux for 1 hour with thionyl chloride (1 ml.), benzene (3 ml.), and pyridine (1 drop). Excess of thionyl chloride was distilled off with the benzene, and the residue dried over soda-lime. The crude acid chloride was dissolved in ether (10 ml.), and the solution added slowly, with stirring, to an ethereal solution of diazomethane (from nitrosomethylurea, 5 g.) at a temperature between 0° and 5°. After 2 hours at room temperature the solvent was removed by evaporation

under reduced pressure. The crude diazo-ketone, which separated as a yellow solid, was heated with acetic acid (10 ml.) on the water-bath for 2 hours. Most of the acid was then distilled off at reduced pressure, and the residue treated with water. Ether-extraction yielded a gum, which on dissolution in warm methanol and cooling, deposited crystals (0·27 g.). Repeated recrystallisation from methanol (charcoal) gave the pure *hexane*, m. p. 99° (Found : C, 74·8; H, 7·8. $C_{22}H_{24}O_4$ requires C, 75·0; H, 7·7%).

(*b*) 3-(*p*-Chloroacetylphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane (Brownlee and Duffin, *loc. cit.*) (3 g.) was refluxed for 2 hours with acetic acid (10 ml.) and fused potassium acetate (4 g.). The acid was then distilled off under reduced pressure, and the residue treated with water and extracted with ether. Evaporation of the washed and dried ethereal solution gave the crude product, which after two recrystallisations from methanol had m. p. 99°, not depressed on admixture with a specimen prepared as above; the yield was 2 g. (Found : C, 75·2; H, 7·7%).

3-(p-2 : 5-*Dihydro*-5-*keto*-3-*furylphenyl*)-4-(p-*methoxyphenyl*)-n-*hexane* (III).—3-(*p*-Acetoxyacetylphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane (2 g.) was mixed with zinc powder (1·9 g.) and dry benzene (20 ml.). The mixture was heated to boiling, and ethyl bromoacetate (3 ml.) in benzene (10 ml.) was added dropwise during 15 minutes, with stirring. More zinc (0·5 g.) was then added, and the mixture heated under reflux for 1 hour. The cooled mixture was treated with dilute sulphuric acid in the usual manner, ether being added to the benzene solution to assist in dispersal of the zinc complex. The benzene solution was washed with water and with sodium hydrogen carbonate solution and then evaporated. The crude reaction product (3·3 g.) was heated under reflux, with stirring, with concentrated hydrochloric acid (20 ml.) and acetic acid (5 ml.) for 1 hour. The mixture was then cooled, and the solid material collected and washed with water. After repeated recrystallisation from benzene (charcoal), the required *ketone* was obtained as colourless plates, m. p. 200° (0·57 g.) (Found : C, 79·0; H, 7·5. $C_{22}H_{24}O_3$ requires C, 78·8; H, 7·5%). By adsorption on alumina and elution with benzene a further 0·28 g. of almost pure product was obtained.

3-(p-2 : 5-*Dihydro*-5-*keto*-3-*furylphenyl*)-4 (p-*hydroxyphenyl*)-n-*hexane* (IV).—(*a*) The crude product from a Reformatsky reaction between ethyl bromoacetate (12·6 g.) and 3-(*p*-acetoxyacetylphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane (9 g.), carried out as described above, was heated under reflux for 4 hours, in an atmosphere of nitrogen, with a 50% solution of hydrogen bromide in acetic acid (100 ml.); after the first 2 hours a further 50 ml. of the hydrogen bromide solution was added. The cooled mixture was poured into ice-water and extracted with benzene. After being washed with sodium hydrogen carbonate solution, the extract was poured on an alumina column. Elution with chloroform yielded a small quantity of yellow oil, which was discarded. Elution with ethyl acetate then yielded a pale yellow oil which rapidly crystallised. Recrystallisation from benzene gave the *butenolide* (IV) (3 g.), m. p. 136° (Found : C, 78·25; H, 7·1. $C_{22}H_{24}O_3$ requires C, 78·5; H, 7·2%).

(*b*) A mixture of zinc powder (1·9 g.) and 3-(*p*-acetoxyacetylphenyl)-4-(*p*-acetoxyphenyl)-*n*-hexane (2 g.) (Biggerstaff and Wilds, *loc. cit.*) was covered with dry benzene (50 ml.), of which 30 ml. were then distilled off. Ethyl bromoacetate (3 ml.) in benzene (10 ml.) was then added, during 10 minutes, with constant stirring to the mixture boiling under reflux. Solid material commenced to separate almost immediately; after 15 minutes, two further portions of zinc powder (0·5 g. each) were added at 5-minute intervals. The mixture was then heated under reflux for 20 minutes and cooled. After treatment in the usual manner with dilute sulphuric acid, the separated benzene solution was evaporated, and the residue (3·4 g.) heated under reflux with stirring for 90 minutes, in an atmosphere of nitrogen, with concentrated hydrochloric acid (50 ml.) and glacial acetic acid (5 ml.). The mixture was poured into water and extracted with ether. The ethereal extract was well washed with sodium hydrogen carbonate solution and evaporated, yielding a gum which crystallised from ethyl acetate–*cyclo*hexane (1·3 g.). Repeated recrystallisation from benzene (charcoal) yielded the pure product (0·86 g.), m. p. 136°, not depressed on admixture with the substance obtained as under (*a*) (Found : C, 78·05; H, 7·1; active H, 0·37. Calc. for $C_{22}H_{24}O_3$: C, 78·5; H, 7·2; active H, 0·30%).

(*c*) 3-(*p*-2 : 5-Dihydro-5-keto-3-furylphenyl)-4-(*p*-methoxyphenyl)-*n*-hexane (III) (0·2 g.) was heated under reflux for 4 hours with a 50% solution of hydrogen bromide in acetic acid (5 ml. plus a further 2·5 ml. after 2 hours). After cooling, water was added, and the solid filtered off. Two recrystallisations from benzene gave the product in colourless prisms (94 mg.), m. p. 136°, not depressed on admixture with the substance obtained as under (*a*) or (*b*).

We thank Miss J. Webster for technical assistance, and the directors of Messrs. Allen and Hanburys Ltd. for permission to publish this work.

RESEARCH DIVISION,
ALLEN AND HANBURYS LTD., WARE, HERTS.

[*Received, December 30th*, 1950.]

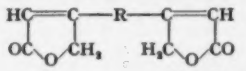
215. *Unsaturated Lactones. Part III. Symmetrical Aromatic Dibutenolides.*

By N. R. Campbell and J. H. Hunt.

Symmetrical *pp'*-dibutenolides have been prepared from diphenyl, diphenyl ether, diphenylmethane, 1 : 2-diphenylethane, stilbene, and 3 : 4-diphenylhexane. The last butenolide is analogous in structure to the synthetic œstrogen, hexœstrol.

The *pp'*-dihydroxy-derivatives of diphenyl, diphenyl ether, diphenylmethane, 1 : 2-diphenylethane, and stilbene were found by Dodds and Lawson (*Proc. Roy. Soc.*, 1938, *B*, **125**, 222) to possess œstrogenic activity. 3 : 4-Di-(*p*-hydroxyphenyl)-*n*-hexane (hexœstrol) (Campbell, Dodds, and Lawson, *Nature*, 1938, **142**, 1121) was found to possess similar activity, but of a very much higher order. More recently, Ross (*J.*, 1945, 536, 538) has published the preparation of a series of methyl ketones and acetoxymethyl ketones, corresponding to the above diphenols and described by him as analogues of progesterone and corticosterone, respectively. Further examples of compounds of the latter type, but related to stilbene and αβ-diethylstilbene, have been described by Hager and Shonle (*J. Amer. Chem. Soc.*, 1946, **68**, 2167) and by Hager and Burgison (*J. Amer. Pharm. Assoc.*, 1950, **39**, 7).

When starting our work on butenolides analogous to the more potent of the synthetic œstrogens, we considered it interesting to prepare the *pp'*-dibutenolide from 3 : 4-diphenylhexane, for comparison with the corresponding *p*-hydroxy-*p'*-butenolide, both of which may be regarded as analogous to hexœstrol. The new butenolides (I)—(VI) have been prepared



(I; R = *pp'*-C_6H_4·C_6H_4·)
(II; R = *pp'*-C_6H_4·O·C_6H_4·)
(III; R = *pp'*-C_6H_4·CH_2·C_6H_4·)
(IV; R = *pp'*-C_6H_4·CH:CH·C_6H_4·)
(V; R = *pp'*-C_6H_4·CH_2·CH_2·C_6H_4·)
(VI; R = *pp'*-C_6H_4·CHEt·CHEt·C_6H_4·)

by lactonising the products from Reformatsky reactions between the corresponding bisacetoxymethyl ketones and ethyl bromoacetate.

pp'-Bisacetoxyacetyl-diphenyl, -diphenyl ether, -1 : 2-diphenylethane, and -3 : 4-diphenylhexane were described by Ross (*loc. cit.*), who prepared them by acetolysis of the corresponding bischloromethyl ketones, obtained by Friedel–Crafts reactions between the appropriate aromatic nucleus and chloroacetyl chloride. We have prepared di-(*p*-chloroacetylphenyl)methane in a similar manner and converted it into the bisacetoxymethyl ketone by treatment with fused potassium acetate in acetic acid. The bischloromethyl ketone was oxidised by chromic acid, yielding benzophenone-*pp'*-dicarboxylic acid, identified by its methyl ester; this confirms the expected di-*para*-substitution in the Friedel–Crafts reaction.

The above procedure is not available for the preparation of *pp'*-bisacetoxyacetylstilbene, since under the conditions of the Friedel–Crafts reaction with chloroacetyl chloride no crystalline product could be isolated (Ross, *loc. cit.*). Accordingly, a pure specimen of the acid chloride of stilbene-*pp'*-dicarboxylic acid (Bell and Waring, *J.*, 1948, 1024) was treated with a solution of diazomethane in benzene, and the crude diazoketone treated with boiling acetic acid, giving the required *pp'*-bisacetoxyacetyl-*trans*-stilbene as a white solid, melting at 206° and clearing at 226°. Hager and Shonle (*loc. cit.*), using an impure acid chloride in a dioxan solution of diazomethane, obtained the bisacetoxymethyl ketone as a yellow solid, m. p. 192—196°.

Purified dioxan was found to be the best solvent in Reformatsky reactions with these ketones, causing better dispersion of the zinc complexes which are formed as the reactions proceed. The crude products from the Reformatsky reactions were generally lactonised without further purification by heating them with hydrogen bromide in acetic acid, or in certain cases with hydrochloric–acetic acids. Lactonisation was frequently accompanied by formation of extremely insoluble amorphous materials, from which the required products were separated by extraction with a powerful solvent, such as *cyclo*hexanone, acetic acid, or nitrobenzene. In the preparation of the dibutenolides of diphenyl and diphenyl ether, the insoluble fraction formed the major part of the crude reaction product. It was not possible to effect purification of these insoluble materials by normal means, but ultimate analyses, carried out on specimens freed as far as possible from extraneous matter, gave results which

indicated empirical formulæ identical with those of the corresponding butenolides. They probably arise from polymolecular condensations of butenolide precursors.

The required dibutenolides were obtained as crystalline solids. Those from diphenyl and stilbene were brightly coloured, the former lemon-yellow, the latter orange. In this, and in their degree of conjugation, they exhibit a resemblance to pulvinic acid dilactone, which has been reported to cause systolic arrest of the isolated frog heart in concentrations of the same order as those required to produce a similar effect with ouabain and digitoxin (Giarman, *J. Pharmacol.*, 1949, **96**, 119). All the new dibutenolides described are very sparingly soluble in physiologically compatible solvents; this has precluded their adequate testing for cardioactivity.

Experimental.

The zinc powder was prepared as described in the preceding paper.

pp′-*Di*-(2 : 5-*dihydro*-5-*keto*-3-*furyl*)*diphenyl* (I.)—4 : 4′-Bisacetoxyacetyldiphenyl (Ross, *loc. cit.*) (9 g.) was mixed with zinc powder (9 g.) and purified dioxan (Hess and Frahm, *Ber.*, 1938, **71**, 2629) (90 ml.) and the whole heated to boiling. Ethyl bromoacetate (8 ml.) was then added slowly as the reaction proceeded, the mixture being heated under reflux for 1 hour. The crude reaction product, obtained as a sticky solid by treating the cooled mixture with dilute sulphuric acid in the usual manner, was dissolved in acetic acid (40 ml.), fuming hydrochloric acid (40 ml.) was added, and the whole heated under reflux for 1 hour, with stirring. A brown solid which separated during the lactonisation was filtered off, dried, and continuously extracted for several hours with boiling *cyclo*hexanone. On cooling, the extract deposited light brown material (1·5 g.). Several recrystallisations from *cyclo*hexanone gave the *dibutenolide* (I) as lemon-yellow needles, decomposing above 320° (Found : C, 75·5; H, 4·5. $C_{20}H_{14}O_4$ requires C, 75·5; H, 4·4%). The *cyclo*hexanone-insoluble *substance* (3 g.) was completely insoluble in a very wide range of solvents. A portion was dried under high vacuum at 150° (Found : C, 74·6; H. 4·7. $C_{20}H_{14}O_4$ requires C, 75·5; H, 4·4%).

pp′-*Di*-(2 : 5-*dihydro*-5-*keto*-3-*furyl*)*diphenyl Ether* (II).—*pp′*-Bisacetoxyacetyldiphenyl ether (Ross, *loc. cit.*) (9 g.) was submitted to a Reformatsky reaction exactly as above but with 16·2 g. of ethyl bromoacetate, and lactonisation was effected by acetic anhydride (50 ml.) and concentrated hydrochloric acid (50 ml.) (vigorous initial reaction). The dark brown solid which separated was filtered off and continuously extracted for several hours with boiling glacial acetic acid. The crude solid obtained by adding water to this extract was filtered off and dried (3 g.). Repeated recrystallisation from *cyclo*hexanone gave the *dibutenolide*, m. p. 243—244° (Found : C, 72·0; H, 4·55. $C_{20}H_{14}O_5$ requires C, 71·9; H, 4·2%). When the product from a similar Reformatsky reaction to the above was heated under reflux with a solution of hydrogen bromide in acetic acid for 90 minutes, a considerable quantity of insoluble material was obtained. This *substance* was also insoluble in a wide range of solvents (Found : C, 72·3; H, 4·6%).

Di-(p-*chloroacetylphenyl*)*methane*.—Diphenylmethane (25 g.) was dissolved in carbon disulphide (150 ml.) and powdered aluminium chloride (50 g.) was added to the stirred mixture. A solution of chloroacetyl chloride (50 ml.) in carbon disulphide (50 ml.) was then added slowly, the flask being cooled in cold water. The mixture was stirred for 1 hour at room temperature, and the decanted carbon disulphide layer discarded. The residue was treated with a mixture of ice and hydrochloric acid, and a yellow solid filtered off. This was crystallised from methanol and repeatedly recrystallised from alcohol (95%). The resulting *di*-(p-*chloroacetylphenyl*)*methane* (10·3 g.) was nearly colourless and of m. p. 123° (Found : C, 63·6; H, 4·6; Cl, 22·9. $C_{17}H_{14}O_2Cl_2$ requires C, 63·55; H, 4·4; Cl, 22·1%).

Oxidation. The above chloro-ketone (0·5 g.) was boiled under reflux for 3 hours with a mixture of sodium dichromate (3 g.) and sulphuric acid (30 ml. of 25% v/v). Water was then added; the precipitated solid, when washed and dried, did not melt below 340°. The dimethyl ester, prepared through the acid chloride had m. p. 225° (Found : C, 68·4; H, 4·8. Calc. for $C_{17}H_{14}O_6$: C, 68·3; H, 4·7%); Limpricht (*Annalen*, 1900, **312**, 92) states that benzophenone-4 : 4′-dicarboxylic acid sublimes without melting below 360° and that the dimethyl ester melts at 225°.

Di-(p-*acetoxyacetylphenyl*)*methane*.—Di-(*p*-chloroacetylphenyl)methane (7·8 g.) was boiled under reflux for 2½ hours with a mixture of acetic acid (32 ml.), acetic anhydride (8 ml.), and fused potassium acetate (10 g.). The mixture was cooled and poured into water (200 ml.), and the solid collected. Several recrystallisations from alcohol (95%) yielded the substituted *diketone* (5 g.), m. p. 114° (Found : C, 68·2; H, 5·8. $C_{21}H_{20}O_6$ requires C, 68·4; H, 5·5%).

Di-(p-2 : 5-*dihydro*-5-*keto*-3-*furylphenyl*)*methane* (III).—A mixture of di-(*p*-acetoxyacetylphenyl)-methane (4·6 g.), zinc powder (4·6 g.), and dioxan (46 ml.) was condensed with ethyl bromoacetate (8·3 g.), and the product worked up in the usual manner. The sticky, solid reaction product was dissolved in acetic acid (30 ml.), and the solution filtered and heated under reflux for 1 hour with concentrated hydrochloric acid (30 ml.). The mixture was cooled and poured into water, and the separated solid dried and recrystallised three times from dioxan (charcoal). The *dibutenolide* (III) (1 g.) had m. p. 256° (Found : C, 75·5; H, 5·0. $C_{21}H_{16}O_4$ requires C, 75·9; H, 4·8%).

pp′-*Bisacetoxyacetylstilbene*.—Stilbene-*pp′*-dicarboxyl chloride (8 g.) (Bell and Waring, *J.*, 1948, 1024) was added portionwise during 2 hours to a solution of diazomethane (from nitrosomethylurea, 30 g.) in benzene (300 ml.), kept at room temperature, and stirred continuously. Next morning, the benzene was distilled off under reduced pressure. The crude crystalline diazo-ketone was added gradually to a boiling mixture of acetic acid (100 ml.) and fused potassium acetate (5 g.). Boiling under reflux was continued for 30 minutes after completion of the addition. After cooling, the mixture was poured into water, and the separated solid washed with sodium carbonate solution, water, and

methanol. Recrystallisation from acetic acid and from toluene gave the stilbene as fine white leaflets (6·5 g.), m. p. 206° to an opalescent liquid clearing sharply at 226° [Hager *et al.* (*loc. cit.*, 1946) report m. p. 192—196°] (Found: C, 69·3; H, 5·35. Calc. for $C_{22}H_{20}O_4$: C, 69·45; H, 5·3%).

pp'-*Di*-(2 : 5-*dihydro*-5-*keto*-3-*furyl*)*stilbene* (IV).—The above acetoxymethyl ketone (5 g.) was subjected to a Reformatsky reaction with ethyl bromoacetate (10 g.) and powdered zinc (5 g.) in dioxan (50 ml.). The reactants were added all at once and the mixture gently heated. After the initial vigorous reaction had subsided, the mixture was boiled under reflux, with stirring for 30 minutes. After cooling, the mixture was decomposed with dilute hydrochloric acid in the usual manner, and the product extracted with ether. The residue on evaporation of the ether was boiled and stirred, under reflux, for 45 minutes with a mixture of acetic acid (20 ml.) and concentrated hydrochloric acid (80 ml.), then poured into water; the yellow, solid product was collected and washed with potassium carbonate solution, water, and methanol. Extraction of this crude material with boiling acetic acid (charcoal) yielded the *dibutenolide* as an orange, microcrystalline powder (2 g.). When heated, this darkened above 300° and decomposed at about 360° (Found: C, 76·2; H, 4·7. $C_{22}H_{16}O_4$ requires C, 76·8; H, 4·7%).

1 : 2-*Di*-(p-2 : 5-*dihydro*-5-*keto*-3-*furylphenyl*)*ethane* (V).—1 : 2-Di(-*p*-acetoxyacetylphenyl)ethane (Ross, *loc. cit.*) (10 g.) was brought into reaction with ethyl bromoacetate (20 g.) and zinc powder (10 g.) in purified dioxan (100 ml.). The reaction was complete after 2 hours' heating, and the cooled mixture was then poured through a glass-wool plug into dilute sulphuric acid. The aqueous solution was decanted from the yellow semi-solid product, which was then heated under reflux, in an atmosphere of nitrogen, for 90 minutes with a 50% solution of hydrogen bromide in acetic acid (50 ml.). After cooling, the mixture was poured into water, and the *dibutenolide* filtered off, washed, dried, and recrystallised repeatedly from glacial acetic acid; m. p. 277° (Found: C, 76·2; H, 5·35. $C_{22}H_{16}O_4$ requires C, 76·25; H, 5·25%).

3 : 4-*Di*-(p-2 : 5-*dihydro*-5-*keto*-3-*furylphenyl*)-n-*hexane* (VI).—*pp'*-Bisacetoxyacetyl-3 : 4-diphenyl-*n*-hexane (Ross, *loc. cit.*) (4·3 g.) was brought into reaction with ethyl bromoacetate (10 g., 3 mols.) and zinc powder (6·5 g., 5 mols.) in dioxan (50 ml.). After being heated under reflux for 1 hour, the reaction mixture was treated in the usual manner, and the crude gummy product (5·5 g.) lactonised by being heated under reflux, in an atmosphere of nitrogen, for 2 hours with a 50% solution of hydrogen bromide in acetic acid (50 ml.). The crude product obtained by pouring the cooled mixture into water was recrystallised repeatedly from glacial acetic acid and then from alcohol by prolonged hot continuous extraction. Final purification was effected by recrystallisation twice from anisole and once from amyl alcohol; the *dibutenolide* formed white, silky needles, m. p. 303° (Found: C, 77·4; H, 6·8. $C_{26}H_{24}O_4$ requires C, 77·6; H, 6·5%).

We thank Miss J. Webster for technical assistance, and the directors of Messrs. Allen and Hanburys Ltd. for permission to publish these results.

RESEARCH DIVISION,
ALLEN AND HANBURYS LTD., WARE, HERTS. [*Received, December 30th*, 1950.]

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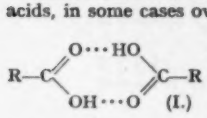
216. *The Characteristic Infra-red Frequencies of the Carboxylic Acid Group.*

By M. ST. C. FLETT.

The infra-red spectra of 60 carboxylic acids, with widely varying structures, have been measured between 700 and 4000 cm.$^{-1}$, to improve the certainty with which a carboxylic acid group can be distinguished from other acidic groups by infra-red spectroscopy. The reliability of five bands as tests for the presence of the carboxy-group has been assessed. For three of these bands it has proved possible to determine the effect of structural changes, such as the introduction of substituents and conjugation with double bonds and ring systems, on the precise frequency of the band. No general relationship between the spectra of acids and their dissociation constants was discovered.

IN recent years infra-red spectroscopy has been used extensively for the detection of chemical groups in materials of unknown structure by observation of characteristic frequencies (Thompson, *J.*, 1948, 328; Williams, *Rev. Sci. Inst.*, 1948, **19**, 135). Deductions may, however, be uncertain if the correlation between the characteristic frequencies and the molecular environment of a group has not been established by measurements on a sufficiently wide variety of compounds. In the case of the carboxylic acid group, many investigators have studied particular acids but no comprehensive investigation of the effect of structure on its characteristic bands seems to have been undertaken, except by Lecomte (" Structure des Molecules " in

" Traité de Chimie Organique," Vol. 2, Masson et Cie, Paris, 1936) who considered only ten acids, in some cases over limited spectral ranges. Sixty carboxylic acids with widely varying structures were therefore examined. The problem is complicated by the dimerisation normally shown by acids in the solid and liquid states giving hydrogen-bonded structures of type (I). The monomers are formed only in dilute solution or in the vapour phase at high temperatures. It was at first thought that the extent of dimerisation in the condensed states might be influenced by bulky substituents close to the carboxy-group, and that it would, therefore, be necessary first to study the effect of structural changes on the bands by examining a series of acids in some solvent in which they were monomeric. Few such solvents are, however, available which are sufficiently transparent at the wave-lengths of the carboxyl group bands. In non-polar solvents, such as carbon tetrachloride (which are spectroscopically most suitable), acids exist as a mixture of monomer and dimer (Davies and Sutherland, *J. Chem. Phys.*, 1938, **6**, 755). Dioxan seemed suitable as it is a good solvent for carboxylic acids, and freezing-point measurements indicate (Lassettre, *Chem. Reviews*, 1937, **20**, 277) that benzoic acid is monomeric in it. This was confirmed by spectroscopic measurement, a single C=O stretching band being observed, whereas two are shown in carbon tetrachloride, corresponding to monomer and dimer. Dioxan was, however, transparent at the wave-lengths of only two of the five bands ultimately associated with the carboxyl group, and acetic acid showed signs of dimerisation in it and also in acetonitrile and chloroform. The idea of examining the frequencies and intensities of the bands of all the acids in the same solvent had, therefore, to be abandoned, though the C=O stretching bands of a number were examined in dioxan. It was decided to examine the liquid acids as thin films and the solids as solid films made by melting or, if the melting points were high, as powders moistened with Nujol to minimise scatter. This procedure has the advantage that the results obtained are more directly applicable to unknown materials, when frequently only a small amount of solid material is available. The spectra of a few low-melting acids were measured as solids and liquids; there were no striking differences, indicating that little would be gained by studying all the liquid acids as solids.



(I.)

Experimental.

The spectra were determined with a Hilger D.209 spectrometer, single-beam photographic recording being used. At those wave-lengths where atmospheric water-vapour absorption interferes, it was necessary to locate the band heads by point-by-point plotting of the " sample " and " background " traces. The wave-lengths were determined either by interpolation among atmospheric water-vapour and carbon dioxide bands where these appeared on the same record, or from calibration charts. Most of the wave-number values listed are believed to be accurate to ± 3 cm.$^{-1}$. Some of the C=O stretching bands near 1700 cm.$^{-1}$ were, however, so broad that the uncertainty is greater, as indicated in the table, and the bands between 2500 and 2700 cm.$^{-1}$ are accurate only to ± 10 cm.$^{-1}$. In the case of the 1700 cm^{-1}. bands studied in dioxan solution, the spectrum of dioxan in the same cell was recorded immediately after each solution was measured. From the two records a graph of optical density against wave number was drawn and the strength of the band determined from this graph (*a*) by calculating the molecular extinction coefficient, ε, and (*b*) by measuring the area under the band with a planimeter. This second procedure did not prove to have any advantage over simple measurement of the peak density.

The acids were mostly commercial samples. If of good appearance with melting point (or boiling point) near the literature values, they were normally used without further purification, since the present work was concerned with strong bands, and small amounts of impurity were unlikely to interfere. Some less common acids had been prepared by colleagues in the Research Department; they were recrystallised and their melting points checked, if low enough to be reliable. The two anhydrous crystalline forms of oxalic acid (Hendricks, *Z. Krist.*, 1935, **91**, 48) were made from the dihydrate; the rhombic form made by recrystallisation from acetic acid (Beilstein, Band 2, p. 505) melted at 180°, and the needle form (Hendricks, *loc. cit.*) was obtained from it by sublimation.

Results.

The table lists the wave numbers of five bands thought to be characteristic of the carboxy-group in each acid examined in the condensed state. The value for the C=O stretching mode in dioxan is also included, with the molecular extinction coefficient, ε, and the dissociation constants of the acids in water.

Discussion.

The acids were chosen to cover as wide a range of structures as possible. Mono- and di-basic aliphatic acids, unsaturated acids, and benzenoid and other aromatic acids were included, but not aliphatic amino-acids, whose zwitterion structure makes their infra-red spectra quite different from that of normal acids. From the band positions it appears that in all cases the solid and liquid acids exist as dimers (or possibly higher polymers) so complications due to monomer–dimer equilibria do not arise.

Previous work made it possible to predict the approximate positions of certain $-CO_2H$

Acid.	Between 2500 and 2700 cm.$^{-1}$.	Near 1700 cm.$^{-1}$. Solid or liquid.	In dioxan.	10^{-2} ε.	Near 1400 cm.$^{-1}$.	Near 1250 cm.$^{-1}$.	Near 900 cm.$^{-1}$.	K.*
Acetic	2570(w), 2660(s)	1712±5	—	—	1415	1293	930(m)	$1{\cdot}86 \times 10^{-5}$
Propionic	2580, 2680(s), 2760	1715±5	1735	4·12	1418	1240	930(m)	$1{\cdot}4 \times 10^{-5}$
Hexanoic	2500(w), 2680(s)	1710±5	1733	5·53	1417	1286, 1245	937(s)	$1{\cdot}43 \times 10^{-5}$
Lauric	2570, 2650(s)	1700±5	—	—	1428	1300	937(s)	—
Chloroacetic	2590, 2700, 2540	1735 (in CCl_4)	—	—	1420±5	1213	933(w)	$1{\cdot}5 \times 10^{-3}$
Cyanoacetic	2530, 2610	1730±5	—	—	1395	1182	935(w)	$3{\cdot}6 \times 10^{-3}$
Phenylacetic	2570, 2650(s), 2740	1697±3	1730	3·21	1409	1230	928, 904(m)	$4{\cdot}88 \times 10^{-5}$
Diphenylacetic	2540, 2640(w), 2720	1695±5	—	—	1410	1225, 1312	937(s)	$1{\cdot}15 \times 10^{-4}$
Phenoxyacetic	2580(s), 2680	1735±5, 1703±5	—	—	1439	1234	915(w)	—
Glycollic	2580, 2640	1730±5, 1710±5	—	—	—	1213	—	$1{\cdot}5 \times 10^{-4}$
Thiolacetic	2590	1710±5	—	—	1420±5	—	—	—
α-Chloropropionic	2570, 2680	1730±10	1745	—	1420	1215	920(w)	$1{\cdot}4 \times 10^{-3}$
β-Chloropropionic	2690, 2590	1710±5	1735	—	1440(w), 1400	1245	932(m)	$1{\cdot}0 \times 10^{-4}$
Lactic	2520, 2630, 2700	1725±5	—	—	—	1225	920(w)	$1{\cdot}38 \times 10^{-4}$
Oxalic (dihydrate)	—	1690—1710	—	—	—	1250	—	—
Oxalic, anhydrous, needle or rhombs...	—	1690—1710	—	—	—	1250	—	—
Malonic	2600, 2700	1740±5, 1710±5	—	—	1422	1311, 1224	920(s)	$1{\cdot}5 \times 10^{-3}$ $2{\cdot}1 \times 10^{-6}$
Succinic	—	1780(w), 1700±5	—	—	1420	1313	923(w)	$6{\cdot}6 \times 10^{-5}$ $2{\cdot}8 \times 10^{-6}$
Adipic	2620	1700±5	—	—	1425	1280	926(s)	$3{\cdot}8 \times 10^{-5}$ $3{\cdot}9 \times 10^{-6}$
Acrylic	2540, 2660	1705±3	—	—	†	1295, 1243	—	$5{\cdot}6 \times 10^{-5}$
Methacrylic	2530, 2610(s), 2700	1700±2	—	—	†	1320	—	—
α-Crotonic	2500, 2680	1700±5	1718	4·34	1438	1312	912(s)	$2{\cdot}03 \times 10^{-5}$
Maleic	2510, 2600	1705±2	—	—	1437	1272	930(w)	$1{\cdot}42 \times 10^{-2}$ $8{\cdot}57 \times 10^{-7}$
Fumaric	2540(s), 2700(w)	1680±5	—	—	1423	1280	932(m)	$1{\cdot}0 \times 10^{-3}$ $4{\cdot}8 \times 10^{-5}$
Benzoic	2580, 2700	1685±5	1720	5·58	1417	1290	935(s)	$6{\cdot}3 \times 10^{-5}$
o-Chlorobenzoic	2540, 2640	1690±2	1733	3·31	1410	1312	917(s)	$1{\cdot}2 \times 10^{-3}$
o-Cyanobenzoic	2530, 2640	1690±5	—	—	1418	1293	910(w)	—
o-Nitrobenzoic	†	1700±3	1730	—	1420	1308	907(w)	$6{\cdot}1 \times 10^{-3}$
Salicylic	2570, 2700	1665±5	1680	—	1440(w)	—	—	$1{\cdot}06 \times 10^{-3}$
Anthranilic (high-temp. form)	2550, 2640, 2710	1670±5	—	—	1420	1240	915(s)	$1{\cdot}05 \times 10^{-6}$
Anthranilic (normal)	2550	1660±5	1697	—	—	—	—	$1{\cdot}05 \times 10^{-5}$
m-Nitrobenzoic	2520, 2580	1690±5	1731	5·65	1412	1288	930(m)	$3{\cdot}44 \times 10^{-4}$

Acid.	Between 2500 and 2700 cm.$^{-1}$.	Near 1700 cm.$^{-1}$. Solid or liquid.	In dioxan.	10^{-4} ε.	Near 1400 cm.$^{-1}$.	Near 1250 cm.$^{-1}$.	Near 900 cm.$^{-1}$.	K.*
p-Nitrobenzoic	†	1690±5	—	—	1430	1308, 1288	935(s)	$4{\cdot}0 \times 10^{-4}$
p-Chlorobenzoic	2550(s), 2640(w)	1685±5	1723	5·52	1425	1322, 1280	928(m)	$1{\cdot}04 \times 10^{-4}$
Anisic	2520, 2630	1685±3	1718	5·05	1428	1300, 1265	935(m)	$3{\cdot}38 \times 10^{-5}$
p-Hydroxybenzoic	2540, 2680	1680±5	1716	4·62	1420	1316, 1240, 1245	930(m)	$2{\cdot}88 \times 10^{-5}$
p-Aminobenzoic	2530, 2650	1670±10	1709	6·22	1420	1314, 1295	926(w)	$1{\cdot}15 \times 10^{-5}$
Mandelic	2530	1715±5	—	—	—	1249	940(w)	$4{\cdot}3 \times 10^{-4}$
Cinnamic	2530, 2660	1680±5	1713	4·62	1420	1311, 1285	940(m)	$3{\cdot}8 \times 10^{-5}$
o-Coumaric	2710(w), 2590, 2530	1665±3	—	—	1430	1220	907(m)	$2{\cdot}10 \times 10^{-5}$
Phthalic	2680, 2540	1695±5	—	—	1403	1282	904(s)	$1{\cdot}26 \times 10^{-3}$
								$5{\cdot}4 \times 10^{-6}$
*tere*Phthalic	2550, 2680	1690±5	—	—	1425	1289	930(s)	—
2 : 4 : 6-Trinitrobenzoic	2540, 2670	1728±3	—	—	1412	1265	928(s)	—
Diphenic	2550, 2640	1685±5	1727	3·77 (per CO_2H)	1407	1284, 1258	920(m)	—
o-Naphthoylbenzoic	2550, 2680	1655—85 ‡	—	—	—	1271	918(m)	—
1-Naphthoic	2520, 2610	1678±3	1717	3·79	—	1284, 1258	—	$2{\cdot}0 \times 10^{-4}$
2-Naphthoic	2570(s), 2660	1690±3	—	—	1423	1307	935(s)	—
3-Hydroxy-2-naphthoic	2550, 2580	1655±5	—	—	1440(w)	1275	905(m)	—
3-Amino-2-naphthoic	—	1665±5	—	—	—	1300, 1270	—	—
Pyromucic	2570, 2680	1690±5	—	—	1428	1301	935(m)	$7{\cdot}1 \times 10^{-4}$
Nicotinic	2490	1700±5	1728	—	1420(w)	1322, 1300	—	$1{\cdot}4 \times 10^{-5}$
Quinaldinic	2510	v. weak	—	—	—	1316	—	—
2-Aminofluorene-9-carboxylic	2620	1700±2	—	—	—	1198	—	—
2-Amino-3-carboxyphenyl 2-hydroxy-4-sulphophenyl sulphone	2610	1660±5	—	—	—	1208	926(w)	—
o-(3-Amino-4-hydroxybenzoyl)benzoic	2560, 2680	1675—95 ‡	—	—	1435	1292	—	—
2-Carboxydiphenylamine	2570, 2650, 2750	1660±5	1690	—	1440, 1412(w)	1260	—	—
Acenaphthene-3-carboxylic	2540, 2590(s)	1665±5	—	—	1440, 1420	1285, 1265, 1245	—	—
3-Hydroxy carbazole-2-carboxylic	2600	1660±5	—	—	—	1315, 1207	902(m)	—
1-Anilinoanthraquinone-2-carboxylic	2570	1660—90 ‡	—	—	1418(w)	1260	935(w)	—
4-Bromo-1-chloroanthraquinone-2-carboxylic	weak	1710 ?‡	—	—	—	1301	—	—

* The values quoted for the dissociation constant, K, were in nearly all cases those given at 25° in the various volumes of Landolt–Börnstein's "Tabellen." Where more than one value was quoted the most recent was normally chosen.

† Not measured in this region.

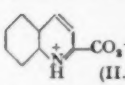
‡ Value uncertain owing to other C=O group in molecule.

bands. Formic, acetic, propionic, and other aliphatic acids have been studied as gases at various temperatures (*e.g.*, Bonner and Hofstatter, *J. Chem. Phys.*, 1938, **6**, 531; Herman and Hofstatter, *ibid.*, p. 534), and in carbon tetrachloride solution (Davies and Sutherland, *loc. cit.*; Buswell, Rodebush, and Roy, *J. Amer. Chem. Soc.*, 1938, **60**, 2239). This work shows that whereas the OH stretching mode of the monomers lies near 3600 cm.$^{-1}$, the dimeric form gives rise to a broad absorption region with many sub-maxima, at 2500—3000 cm.$^{-1}$. The reason for its great breadth has been discussed by Davies and Sutherland (*loc. cit.*). Similarly band pairs at 1768 and 1719 cm.$^{-1}$ and at 1378 and 1442 cm.$^{-1}$, observed in carbon tetrachloride solutions, are associated, respectively (Davies and Sutherland, *loc. cit.*), with the C=O stretching and C–O– stretching vibrations in the monomeric and dimeric forms. Lecomte (" Structure des Molecules " in " Traité de Chimie Organique," Vol. 2, Masson et Cie, Paris, 1936) mentions a band between 945 and 930 cm.$^{-1}$.

In agreement with the above, bands were observed in most of the acids at 2500—3000 cm.$^{-1}$, near 1700 cm.$^{-1}$, and near 1400 cm.$^{-1}$. Also most of the spectra had their strongest band in the 700—1600-cm.$^{-1}$ range between 1200 and 1300 cm.$^{-1}$. This band and another near 900 cm.$^{-1}$ are listed in the table.

The 2500—3000-cm.$^{-1}$ band is often modified by the C–H stretching bands which occur at 2800—3100 cm.$^{-1}$. A sub-group of one to three bands, however, appears between 2500 and 2700 cm.$^{-1}$ (with the resolution achieved by a rock-salt prism), as in the table. These are not overlaid by C–H bands, and accordingly show up well even in " Nujol " mulls of solid acids. The only acids studied which did not show these sub-bands were oxalic, succinic, and 3-amino-2-naphthoic acid. The first two did, however, show the broad absorption region between 2500 and 3000 cm.$^{-1}$. Oxalic acid was also unique in that its hydrate and both anhydrous forms showed a peak near 3400 cm.$^{-1}$. The two anhydrous forms did not show any spectral difference which could be interpreted in terms of their different crystal structures (Pauling, " Nature of the Chemical Bond," p. 309). The sample of 3-amino-2-naphthoic acid melted at 215—216° (literature 214°). Since 2500—2700 cm.$^{-1}$ is a range where bands due to other groups seldom occur, the bands in the range provide perhaps the surest way of detecting a carboxy-group. The absolute intensity of the band is not, however, very great, and the band might be too weak for detection in acids of very high molecular weight (> 300—400). No conclusions could be reached regarding the effect of structure on the number and exact frequencies of the peaks in this region.

A strong band occurs near 1700 cm.$^{-1}$ in the spectrum of every acid examined, except quinaldinic acid, which possibly occurs in the solid state as the zwitterion (II), though this would apparently lead to a loss of resonance energy. Although this is the strongest of the carboxy-group bands, its usefulness in diagnosis is limited, since aldehydes, ketones, and possibly esters may absorb at this wave-length. The influence of structure is clearly reflected in the exact position of this band. Normally, it is higher than 1700 cm.$^{-1}$ for aliphatic and lower for aromatic acids. In only two acids where the carboxy-group is directly attached to an aromatic nucleus (*o*-nitrobenzoic and 2 : 4 : 6-trinitrobenzoic acid) is the value greater than 1700 cm.$^{-1}$; both contain the powerfully electron-attracting nitro-group. Only three acids (phenylacetic, diphenylacetic, and cinnamic), which might be regarded as aliphatic, have the band below 1700 cm.$^{-1}$. Of the five acids having unusually high values (>1725 cm.$^{-1}$), three (chloroacetic, α-chloropropionic, and 2 : 4 : 6-trinitrobenzoic) have electron-attracting substitutents. Of the nine in which the band is below 1680 cm.$^{-1}$, seven (salicylic, anthranilic, *o*-coumaric, 3-hydroxy-2-naphthoic, 3-amino-2-naphthoic, 3-hydroxycarbazole-2-carboxylic acid, and 2-carboxydiphenylamine) are capable of internal hydrogen bonding. Phenoxyacetic, glycollic, succinic, and malonic acids show two bands in this region; two of these acids are dibasic, but there is no evidence that this is a general property of dibasic acids. It is clear that once the presence of the carboxy-group is established, further information about the structure of the acid is obtainable from the precise value of the C=O stretching frequency.


(II.)

This band was also studied in dioxan solutions of some acids. The possibility of correlating both the frequency and the intensity of the band in the monomeric acid with the structure and dissociation constant of the acid was considered. Provided that the structural changes are not very great (*e.g.*, the introduction of substituents into benzoic acid), a reasonably good correlation is observed between frequency, dissociation constant, and the electron-attracting or -donating power of the substituent (Flett, *Trans. Faraday Soc.*, 1948, **44**, 767). A similar correlation was observed by Gilette (*J. Amer. Chem. Soc.*, 1936, **58**, 1143) for various methyl- and halogen-substituted acetic acids. There is, however, no evidence for a comprehensive relationship

between frequencies and dissociation constants; presumably the entropies of ionisation vary if the structural changes are considerable.

No regular effect of substitution on the extinction coefficient was deduced. The average value of ε for 18 acids was 464, but individual values are considerably spread around this figure.

Examination of the table shows that the 1400-cm.$^{-1}$ band is less useful for diagnosis than the two already discussed. It has not been observed in 15 acids. This is partly because it is intrinsically weaker, and is at a wave-length where it is likely to be overlaid by other strong bands. Though the evidence is not very strong, it appears that structural changes affect this band in the opposite direction to changes in the C=O stretching band. Thus, of six acids in which it is unusually high (>1430 cm.$^{-1}$), four are unsaturated or internally hydrogen-bonded (salicylic acid, 2-carboxydiphenylamine, maleic acid, crotonic acid), whereas of the eight in which it is below 1415 cm.$^{-1}$, four (*m*-nitrobenzoic, *o*-chlorobenzoic, 2 : 4 : 6-trinitrobenzoic, and β-chloropropionic) have electron-attracting substituents. A similar observation was made previously in the case of substituted benzoic acids (Flett, *Trans. Faraday Soc.*, 1948, **44**, 767).

The position of the 1250-cm.$^{-1}$ band varies widely from compound to compound, but the general influence of structure on it can be discerned. Of 18 acids where it is above 1280 cm.$^{-1}$, fourteen are aromatic and two more are unsaturated. Of the ten in which it is below 1240 cm.$^{-1}$ (lactic, phenoxyacetic, phenylacetic, cyanoacetic, glycollic, chloroacetic, α-chloropropionic, *o*-coumaric, 2-aminofluorene-9-carboxylic acid, and 2-amino-3-carboxyphenyl 2-hydroxy-4-sulphophenyl sulphone) six are substituted acetic acids. Esters and ketones (Thompson and Torkington, *J.*, 1945, 640) have bands near 1250 cm.$^{-1}$; this limits the usefulness of the band in diagnosis.

The band between 900 and 940 cm.$^{-1}$ was observed in the spectra of 43 acids, and its appearance is unlikely to be coincidental. There is no apparent correlation of its appearance and non-appearance, or of its precise frequency, with structural factors. The band might, on occasion, provide some confirmation of a carboxy-group detected by its other bands.

There are thus five bands to be considered in detecting a carboxy-group. The peak optical densities of the bands at 2500—2700 cm.$^{-1}$, near 1700 cm.$^{-1}$, near 1420 cm.$^{-1}$, near 1250 cm.$^{-1}$, and near 900 cm.$^{-1}$ were estimated to be very roughly in the ratio 1 : 5 : 2 : 3 : 1. The first two are the most highly characteristic and if neither can be detected, the substance is unlikely to be an acid. In doubtful cases the other three bands provide confirmatory evidence, though the absence of any of them does not imply the absence of a carboxy-group. Some information about the structure of the acid can be deduced from the precise frequencies of these bands. Conjugation with aromatic nuclei, internal hydrogen bonding with hydroxy- or amino-groups, and to a lesser extent conjugation with ethylenic double bonds lower the C=O stretching frequency, whereas electron-attracting substituents raise it. These influences seem to have the opposite effect on the bands near 1420 cm.$^{-1}$ and 1250 cm.$^{-1}$.

There appears not to be any sure means of distinguishing between monobasic and dibasic acids. Even in cases such as phthalic, maleic, and malonic acids, where the two carboxy-groups are in close proximity and would be expected to bond internally, the band positions are fairly normal.

The carboxy-group does not normally interfere with the characteristic frequencies of other groups. Of the unsaturated acids examined, maleic, acrylic, methacrylic, crotonic, cinnamic, and *o*-coumaric show respectively bands at 1635, 1640, 1640, 1630, 1635, and 1620 cm.$^{-1}$, which may plausibly be associated with the C=C stretching vibrations. Fumaric acid shows no outstanding band in this region. This may be connected with the centre of symmetry in the molecule which would render the C=C stretching band weak in the infra-red. Crotonic, cinnamic, and *o*-coumaric acids show bands respectively at 974 cm.$^{-1}$, 980 cm.$^{-1}$, and 990 cm.$^{-1}$ which are associated with bending of the C–H bond in *trans*-symmetrically disubstituted ethylenes (Sheppard and Sutherland, *Proc. Roy. Soc.*, 1949, *A*, **196**, 195). The band at 982 cm.$^{-1}$ in acrylic acid may be similarly explained. Hydroxy- and amino-groups in acids can readily be detected, since the 2500—3100-cm.$^{-1}$ acid absorption does not overlie the highly characteristic OH and NH bands. All the acids with an imino- or amino-group (except 1-anilinoanthraquinone-2-carboxylic acid) had bands between 3500 and 3250 cm.$^{-1}$, and all the hydroxy-acids (except glycollic) had a discrete band between 3500 and 3200 cm.$^{-1}$. The benzoic acids examined do not show bands in the region 700—850 cm.$^{-1}$ characteristic of *o*-, *m*-, and *p*-substitution. The nitro-acids showed the characteristic nitro-group bands near 1350 and 1550 cm.$^{-1}$.

I am grateful to Mr. A. E. Clough for experimental assistance.

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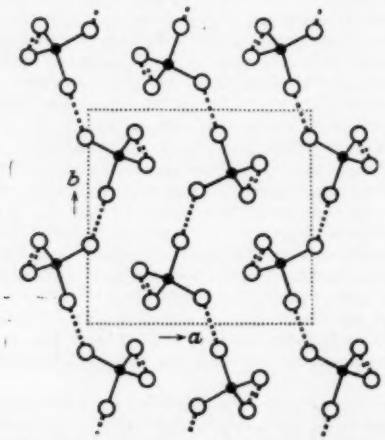
217. *The Structures of Inorganic Oxy-acids: The Crystal Structure of Selenic Acid.*

By M. Bailey and A. F. Wells.

The crystal structure of anhydrous selenic acid, H_2SeO_4, has been determined. The crystals are orthorhombic: $a = 8{\cdot}52$, $b = 8{\cdot}17$, $c = 4{\cdot}61$ A., with 4 molecules in the unit cell. The space-group was taken as $P2_12_12_1$, though three very weak reflexions (700, 090, and 001) were observed on heavily-exposed photographs. The structure consists of tetrahedral SeO_4 groups (mean Se–O, 1·61 A.), each joined by four O–H–O bonds (lengths 2·61 and 2·68 A.) to four neighbouring groups to form puckered layers parallel to (100).

In describing the crystal structure of the orthorhombic form of selenious acid, H_2SeO_3 (*J.*, 1949, 1282), we remarked that very little is known of the structures of crystalline oxy-acids H_mXO_n, the only other structure which had been determined being that of α-iodic acid (Rogers and Helmholz, *J. Amer. Chem. Soc.*, 1941, **63**, 278). When these acids are classified according to the value of the H : O ratio, $r_{H:O}$, they fall into four classes: (*a*), $r_{H:O} < \frac{1}{2}$, *e.g.*, HIO_3, $H_2S_2O_7$;

Fig. 1.



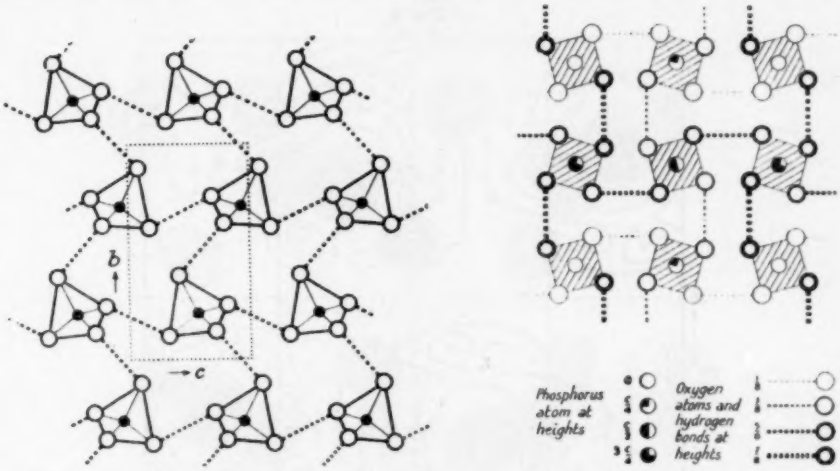
The crystal structure of selenic acid projected on (001). *The small black circles represent* Se *atoms. The puckered layers of* SeO_4 *groups linked by* O–H–O *bonds (heavy broken lines) are perpendicular to the plane of the paper. The pairs of short* O–H–O *bonds form links to oxygen atoms of* SeO_4 *groups situated above and below those shown.*

(*b*), $r_{H:O} = \frac{1}{2}$, *e.g.*, H_2SO_4, H_2SeO_4; (*c*) $1 > r_{H:O} > \frac{1}{2}$, *e.g.*, H_2SeO_3, H_3PO_4, and (*d*) $r_{H:O} = 1$, *e.g.*, H_3BO_3, H_6TeO_6. Since the hydrogen atoms link up the XO_n groups in these crystals by means of O–H–O bonds, as in "acid-salts" such as $NaHCO_3$ and KH_2PO_4, the ratio $r_{H:O}$ determines the type of hydrogen-bonded network. If $r_{H:O} = \frac{1}{2}$ there can be one O–H–O bond to each oxygen atom, as is found in crystals of KH_2PO_4 and $(NH_4)_2H_2IO_6$, and if $r_{H:O} = 1$ there can be two O–H–O bonds to each oxygen atom, as in crystalline H_3BO_3. In KH_2PO_4 the hydrogen-bonded network $[H_2PO_4]^-_\infty$ is a three-dimensional framework, in the interstices of which the K^+ ions are situated. It was pointed out in the earlier paper that the structure of crystalline H_2SO_4 may be closely related to this $[H_2PO_4]^-_\infty$ framework in KH_2PO_4 and isomorphous salts.

As an example of an oxy-acid H_2XO_4, selenic acid was chosen in preference to sulphuric acid, with which it is likely to be isomorphous, since it is solid at room temperature. Owing to their

relatively high scattering power for *X*-rays, the selenium atoms can be readily located, but for the same reason the determination of the precise positions of the oxygen atoms is rendered more difficult. More accurate hydrogen-bond lengths could probably be obtained from a study of crystalline sulphuric acid. However, the crystal structure of anhydrous selenic acid has now been determined with sufficient accuracy to indicate without ambiguity the nature of the hydrogen-bonded network. Each tetrahedral SeO_4 group is linked by four O–H–O bonds to four neighbouring groups to form puckered layers which are viewed end-on in Fig. 1. (It is interesting that the orthorhombic form of selenious acid also has a layer structure.) A projection of the crystal structure of selenic acid normal to the plane of the layers is very similar to that of the $[H_2PO_4]_\infty^-$ framework of KH_2PO_4, as is seen from Fig. 2. In the latter crystal,

FIG. 2.



(*a*) *Projection on* (100) *of one layer of the crystal structure of selenic acid.*

(*b*) *Projection on* (001) *of the structure of* KH_2PO_4.

however, this hydrogen-bonded framework extends indefinitely in three dimensions, in contrast to the layer structure of H_2SeO_4.

The Crystal Structure of Selenic Acid.

An aqueous solution of selenic acid was prepared by treating an aqueous suspension of silver selenite with the calculated quantity of bromine and filtering off the silver bromide. The anhydrous acid was obtained by distilling off the water under reduced pressure, the temperature being taken finally to 150°. It was not possible to grow suitable crystals from the molten anhydrous acid, and the method adopted was to allow a little moisture to enter the stoppered tube which was then warmed slightly. On cooling, needles elongated along the *c* axis were obtained. For the *X*-ray work needles (or portions of needles) were quickly transferred to thin-walled glass capillaries previously sealed at one end, the other end being sealed when the crystal had been suitably oriented.

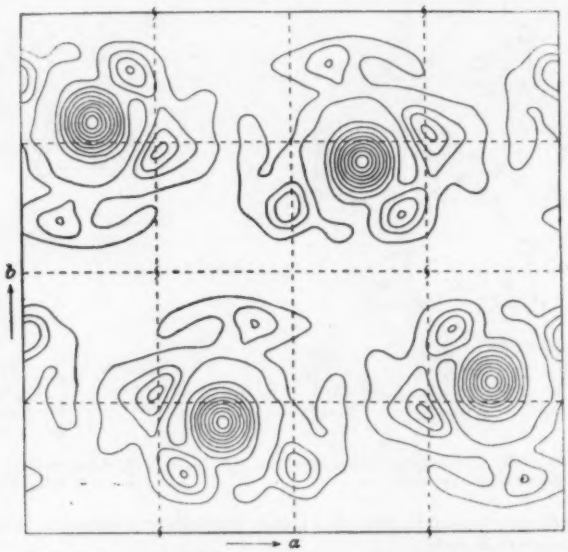
Unit Cell and Space-group.—Oscillation photographs taken with the crystal rotating about the principal axes showed that the crystals are orthorhombic. Zero layer-line Weissenberg photographs were taken about the *a* and *b* axes, and zero and first layer-line photographs about the *c* axis, all with Cu-K_α radiation. The cell dimensions are: $a = 8{\cdot}52 \pm 0{\cdot}02$ A., $b = 8{\cdot}17 \pm 0{\cdot}02$ A., and $c = 4{\cdot}61 \pm 0{\cdot}01$ A., and this cell contains 4 molecules of H_2SeO_4 [density: calc., 3·00 g./c.c.; obs. (Landolt–Börnstein), 2·95 g./c.c.]. The systematic absences are the odd orders of *h*00, 0*k*0, and 00*l*, except that very weak reflexions 700, 090, and 001 were observed on photographs of very long exposure. These have been neglected, and the space-group taken as $P2_12_12_1$. Intensities were estimated visually by using the multiple film method and comparison

with a time-calibrated scale of exposures, and they were converted into structure amplitudes by applying the appropriate correction factors.

Determination of Structure.—Apart from the hydrogen atoms (which cannot be located directly from the *X*-ray data), there are five sets of atoms (Se, O_1, O_2, O_3, and O_4) in four-fold general positions *xyz*, etc. The co-ordinates of the selenium atoms were determined first.

(a) *Selenium co-ordinates.* A close-packed arrangement of SeO_4 groups was considered probable, and would require *x* and *y* co-ordinates for Se of approximately $\frac{1}{8}$ and $\frac{1}{4}$, respectively. The intensities of the *h*00 and 0*k*0 reflexions were consistent with these values. The approximate value of z_{Se} and more accurate values of x_{Se} and y_{Se} were obtained from F^2-projections on (001) and (010). From the structure amplitudes of high-order reflexions and later Fourier projections the best Se co-ordinates were found to be : $x_{Se} = 0{\cdot}369$, $y_{Se} = 0{\cdot}212$, and $z_{Se} = 0{\cdot}563$.

FIG. 3.



Electron-density projected on (001) *showing selenium atoms surrounded by four oxygen atoms.*

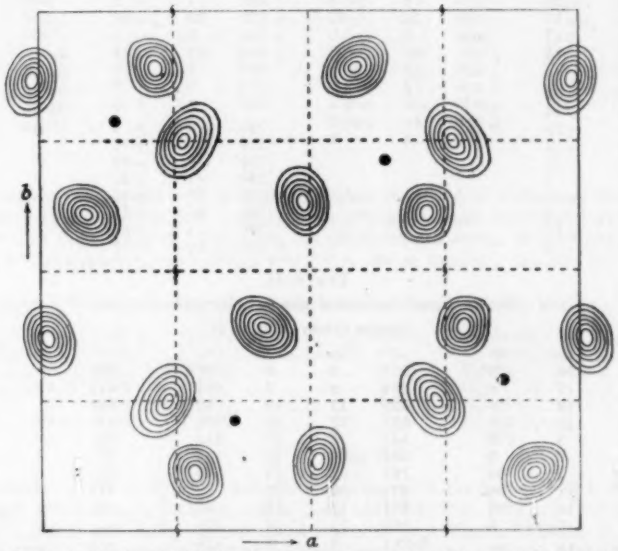
(b) *Oxygen* x *and* y *co-ordinates.* The structure was first projected along the *c* axis because (1) overlapping of atoms is less likely owing to the short length of this axis, and (2) errors due to absorption are smaller for (*hk*0) than for (*h*0*l*) or (0*kl*) reflexions when the crystals are needles elongated along the *c* axis. The origin for *c*-axis projections was taken at the point ($\frac{1}{4}$, 0, 0) about which the projection is centro-symmetrical. The signs of 57 structure amplitudes were determined, the selenium co-ordinates given above being used, and these terms were used for the first projection. Successive refinements were carried out with an artificial temperature factor, $e^{-2[(\sin\theta)/\lambda]^2}$ applied to $F_{obs.}$ to reduce errors due to the slow convergence of the series. The final projection of this set is shown in Fig. 3. The resolution and regularity of the oxygen peaks was not satisfactory, and a further synthesis was therefore computed by using the actual values of $F_{obs.}$ including values of F_{Se} for planes outside the range of the photograph having spacings down to 0·5 A. This appeared reasonable because the Se co-ordinates are known fairly accurately and because the oxygen scattering is negligible at high angles. The diffraction effects around the Se atoms which can be seen in Fig. 3 were considerably reduced in this projection, but the contours of the oxygen peaks were still rather irregular.

The final *x* and *y* co-ordinates were derived from projections for which the series was made much more rapidly convergent by using only that part of each observed F_{hk0} which was due to the oxygen atoms. The selenium contributions were calculated using the normal *f*-curve

modified by a temperature factor $e^{-0.5[(\sin\theta)/\lambda]^2}$ appropriate to this structure and were subtracted (algebraically) from the respective F_{M0}'s which had been converted approximately into absolute values by comparison with calculated values. The resulting F_{M0}'s should then correspond to the selenic acid structure from which the Se atoms have been removed. The projection obtained in this way is shown in Fig. 4.

(c) *Oxygen z co-ordinates.* The projections of the structure on (010) and (100) gave only approximate oxygen co-ordinates because of overlapping of the atoms and probably also because of inaccurate intensity data due to absorption. (Crystals used for [*a*] and [*b*] axis photographs were elongated along [*c*]; it was found impossible to cut equidimensional portions of crystals owing to cleavage(s) along the needle direction.) The oxygen *z* co-ordinates obtained from these projections were refined by line syntheses normal to (001), applying an artificial temperature factor $e^{-4[(\sin\theta)/\lambda]^2}$ to the values of $F_{obs.}$. For the calculation of phase angles the *z*

FIG. 4.



Electron-density projection [*on* (001)] *showing oxygen atoms only. The small black circles indicate the positions of the selenium atoms.*

co-ordinates of the oxygen atoms were taken as the means of the values obtained from the (010) and (100) projections. The final atomic co-ordinates, expressed as fractions of the cell edges, are:

	x/*a*.	*y*/*b*.	*z*/*c*.		*x*/*a*.	*y*/*b*.	*z*/*c*.		*x*/*a*.	*y*/*b*.	*z*/*c*.
Se	0·369	0·212	0·563	O_2 ...	0·285	0·108	0·321	O_4	0·415	0·390	0·411
O_1	0·513	0·128	0·714	O_3 ...	0·235	0·252	0·808				

The structure amplitudes calculated from these co-ordinates and incorporating a temperature factor $e^{-0.5[(\sin\theta)/\lambda]^2}$ are listed in Tables I—III. The atomic *f* curves used were those of the International Tables (Vol. 2, p. 571) for Se and O atoms, the H atoms being neglected. For the *hk*0 reflexions the value of the function $\Sigma(F_{obs.} - F_{calc.})/\Sigma F_{obs.} = 0{\cdot}12$ and, for *hkl* reflexions, 0·16. It has not been calculated separately for *h*0*l* or 0*kl* reflexions for which the values of $F_{obs.}$ are less reliable owing to absorption. Values of $F_{obs.}$ which are seriously reduced owing to absorption are enclosed in parentheses in Tables II and III.

Description of the Structure.—The general nature of the structure has already been mentioned. The distances between oxygen atoms of different SeO_4 groups fall into two groups. Four of the O–O contacts of any SeO_4 groups (two of 2·61 A. and two of 2·68 A.) are much shorter than the rest, which are 2·95 A. or more. The number of these short O–O distances is the number of

TABLE I.

Observed and calculated structure amplitudes (hk0).

[Origin taken at (¼, 0, 0.]

	$F_{obs.}$	$F_{calc.}$		$F_{obs.}$	$F_{calc.}$		$F_{obs.}$	$F_{calc.}$		$F_{obs.}$	$F_{calc.}$
020	66	−61	310	11	+ 9	510	14	−10	800	34	+33
040	10	+10	320	16	−14	520	10	−10	810	10	+ 5
060	14	−17	330	12	+10	530	29	+21	820	30	−28
080	4	+ 4	340	25	+24	540	21	−21	830	18	−18
0.10.0	17	+19	350	32	−35	550	31	−24	840	15	+16
110	11	+15	360	28	−28	560	27	+27	850	9	+ 9
120	21	−24	370	22	+21	570	25	+22	860	3	− 3
130	25	−26	380	22	+21	580	7	− 9	870	5	+ 6
140	28	+28	390	8	− 8	590	17	−17	910	6	+ 6
150	24	+25	3.10.0	10	−10	600	6	− 2	920	9	−10
160	23	−21	400	31	−30	610	42	+38	930	16	−14
170	20	−22	410	9	− 3	620	7	+ 5	940	9	+ 8
180	13	+17	420	34	+31	630	34	−30	950	20	+21
190	13	+17	430	2	0	640	5	− 3	960	4	− 6
1.10.0	10	−13	440	25	−24	650	13	+13	10.00	9	+ 4
200	13	+10	450	<3	+ 3	660	4	− 5	10.10	21	−18
210	53	−62	460	<3	0	670	5	+ 3	10.20	12	−10
220	14	−14	470	<3	− 1	680	5	+ 4	10.30	16	+16
230	20	+25	480	14	+15	710	4	+ 4	10.40	10	+11
240	13	+14	490	4	+ 2	720	20	+16			
250	11	−11				730	12	−10			
260	6	− 7				740	27	−20			
270	3	+ 1				750	13	+13			
280	<3	+ 1				760	25	+21			
290	14	+15				770	8	−10			
2.10.0	<2	− 2				780	16	−19			

TABLE II.

Observed and calculated structure amplitudes (hkl).

[Origin taken at (0, 0, 0).]

	$F_{obs.}$	$F_{calc.}$	α.		$F_{obs.}$	$F_{calc.}$	α.		$F_{obs.}$	$F_{calc.}$	α.
011	43	59	270°	301	5	5	90°	601	30	30	270°
021	15	17	0	311	9	9	168	611	15	12	323
031	15	19	90	321	13	10	72	621	31	27	81
041	15	15	180	331	22	19	356	631	19	16	136
051	8	8	270	341	25	27	215	641	19	17	259
061	9	9	0	351	24	24	185	651	9	6	318
071	<4	1	90	361	21	24	356	661	5	2	74
081	6	8	180	371	22	22	13	671	8	8	198
091	11	14	90	381	12	15	35	681	10	8	100
0.10.1	6	7	0	391	15	16	201	701	28	25	90
101	16	18	90	3.10.1	9	8	329	711	15	13	211
111	13	17	17	401	6	4	270	721	16	12	245
121	19	19	332	411	41	43	98	731	22	18	157
131	34	35	201	421	14	10	139	741	12	11	357
141	24	25	166	431	29	30	273	751	22	19	350
151	27	29	27	441	15	11	329	761	9	13	205
161	23	24	5	451	17	12	65	771	23	19	175
171	16	19	173	461	16	12	181	781	9	10	30
181	14	18	182	471	4	2	123	801	7	3	90
191	9	13	3	481	15	12	4	811	26	23	268
1.10.1	14	12	15	491	13	12	261	821	11	10	318
201	(33)	63	90	501	9	8	270	831	19	19	86
211	5	5	218	511	15	11	278	841	10	11	135
221	33	45	298	521	22	17	152	851	8	7	247
231	10	10	357	531	11	9	346	861	6	6	20
241	14	18	79	541	28	23	333	871	5	4	315
251	13	13	185	551	23	22	173	901	<4	1	90
261	9	13	213	561	22	22	172	911	12	7	59
271	11	13	13	571	14	15	358	921	12	13	352
281	7	6	248	581	21	19	7	931	10	9	141
291	7	8	194	591	8	9	144	941	19	16	179
2.10.1	20	18	75					951	8	8	356
								10.01	21	20	90
								10.11	9	6	69
								10.21	20	19	269
								10.31	10	8	284
								10.41	12	14	80

TABLE III.

Observed and calculated structure amplitudes (h0l and 0kl).

[For *h0l* origin is taken at (0, 0, ¼) and for *0kl*, at (0, ¼, 0).]

	$F_{obs.}$	$F_{calc.}$		$F_{obs.}$	$F_{calc.}$		$F_{obs.}$	$F_{calc.}$		$F_{obs.}$	$F_{calc.}$
002	14	−15	004	5	− 1	012	14	+12	014	10	+12
102	10	+ 7	104	22	−31	022	18	+20	024	2	+ 1
202	5	− 4	204	3	+ 2	032	(17)	+23	034	(14)	+20
302	16	+21	304	7	−10	042	(10)	+18	044	(<3)	+ 1
402	(22)	+43	404	4	+ 4	052	(17)	+22	054	(13)	+21
502	(17)	−31	504	(11)	+18	062	2	− 1	064	2	− 1
602	2	− 3	604	(<2)	+ 4	072	24	+20	074	22	+24
702	6	− 7	704	9	+11	082	12	−12			
802	16	−13	804	2	+ 2	092	20	+16	015	10	+12
902	17	+18							025	(9)	−16
10.02	7	+ 7	105	11	+18	013	11	−12	035	(8)	+13
			205	9	−11	023	18	−19	045	13	−16
103	15	−14	305	(10)	−18	033	(13)	−24	055	6	+ 8
203	9	−10	405	(<2)	− 5	043	(14)	−23			
303	22	+32	505	6	− 8	053	(6)	−12			
403	4	− 4				063	19	−12			
503	(8)	+13				073	3	+ 3			
603	(7)	+15				083	25	−24			
703	20	−20				093	3	+ 3			
803	14	− 9									
903	7	− 9									

hydrogen atoms in the crystal and they are therefore regarded as indicating O–H–O bonds. These link each SeO_4 group to four neighbouring groups to form puckered layers parallel to (100), as shown in Figs. 1 and 2. Including the three oxygen atoms of the same SeO_4 group, the numbers of neighbours up to a distance of 3·5 A. are as follows: O_1, 10; O_2, 12; O_3 and O_4, 11.

The interatomic distances and interbond angles within the SeO_4 group are:

Se–O_1	1·57 A.	O_1–O_2	2·66 A.	O_1–Se–O_2	116°
Se–O_2	1·57	O_1–O_3	2·61	O_1–Se–O_3	109
Se–O_3	1·64	O_1–O_4	2·68	O_1–Se–O_4	112
Se–O_4	1·66	O_2–O_3	2·66	O_2–Se–O_3	112
		O_2–O_4	2·59	O_2–Se–O_4	106
Mean	1·61	O_3–O_4	2·64	O_3–Se–O_4	106
		Mean	2·64	Mean	110°

The Se–O distance of 1·61 A. in SeO_4^{2-} may be compared with the values 1·73 A. and 1·78 A. in crystalline SeO_2 (McCullough, *J. Amer. Chem. Soc.*, 1937, **59**, 789), 1·72 A. in the orthorhombic form of H_2SeO_3 (Wells and Bailey, *loc. cit.*), and 1·61 A. in SeO_2 vapour (Palmer, *J. Amer. Chem. Soc.*, 1938, **60**, 1309). It is interesting that the bond length Se–O is the same in the SeO_2 molecule as in the SeO_4^{2-} ion of H_2SeO_4, whereas for 3-covalent Se in crystalline SeO_2 and H_2SeO_3 the distance is appreciably greater. In the case of sulphur the S–O distance is the same in the SO_2 molecule as in SO_4^{2-} (close to 1·45 A.) but also the same for 3-covalent sulphur in the $S_2O_5^{2-}$ ion (1·45 A.) (Zachariasen, *Physical Rev.*, 1932, **40**, 923). The value, 1·39 A., found in the SO_3^{2-} ion in Na_2SO_3 (Zachariasen and Buckley, *ibid.*, 1931, **37**, 1295) may be rather less accurate than the value from the carefully determined $K_2S_2O_5$ structure. This difference between sulphur and selenium is not unexpected, for there are many differences between the oxygen chemistries of these two elements; for example, whereas sulphur and tellurium form trioxides, selenium does not, and it is interesting that the next element in the same row of the Periodic Table, bromine, also does not form many types of oxy-compound formed by chlorine and iodine.

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[*Received, October 6th*, 1950.]

218. *Deoxy-sugars. Part XIV. A Further Contribution to the Chemistry of 2-Deoxy-D-galactose.*

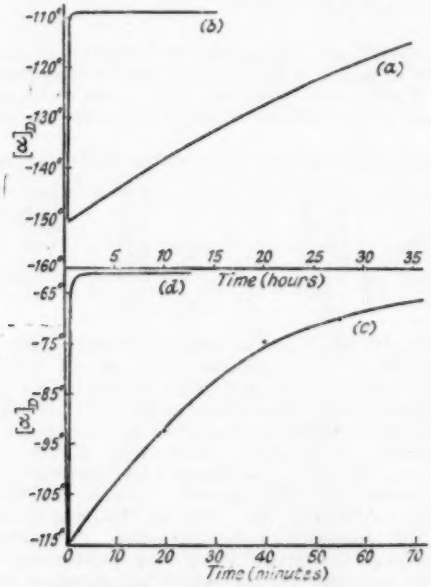
By A. B. Foster, W. G. Overend, and M. Stacey.

A study of the properties and reactions of 2-deoxy-D-galactose has been extended (cf. *J.*, 1950, 671). Numerous new derivatives are described and compounds suitable as intermediates for the preparation of phosphoric acid derivatives of 2-deoxy-D-galactose have been prepared and their structures established. The action of ethanolic hydrogen chloride on the deoxyhexose has been investigated.

Investigations during recent years have shown, increasingly, that the rôle of sugar phosphates in biological processes is of great importance. For example, the phosphoric acid derivatives of D-ribose and its 2-deoxy-analogue form significant elements in the structure of nucleic acids. An understanding of the biological action of these macromolecules must involve a detailed study of their building units. We have already described some experiments of this nature

Fig. 1.

Mutarotation of 2-deoxy-D-galactose p-toluidide.



(*a*) *In pyridine* (c, 1·0).
(*b*) *As* (*a*) *with* 0·1N-H_2SO_4 (*one drop*) *added.*
(*c*) *In methanol* (*c*, 1·0).
(*d*) *As* (*c*) *with* 0·1N-H_2SO_4 (*one drop*) *added.*

and, in this and the following two communications, the preparation and properties of phosphoric acid derivatives of some 2-deoxy-sugars are described. Because of its availability and the crystalline nature of its derivatives, 2-deoxy-D-galactose has again been used in these model reactions. Of the components of deoxyribonucleic acid, 2-deoxy-D-ribose-3 and -5 phosphoric acid are important members. Since in the former compound the hydroxyl group adjacent to the methylene group is esterified by phosphoric acid and in the latter it is the primary hydroxyl group which is esterified, we expect some differences in their chemical stabilities. With 2-deoxy-D-galactose the corresponding derivatives are the 3- and the 6-phosphoric acids.

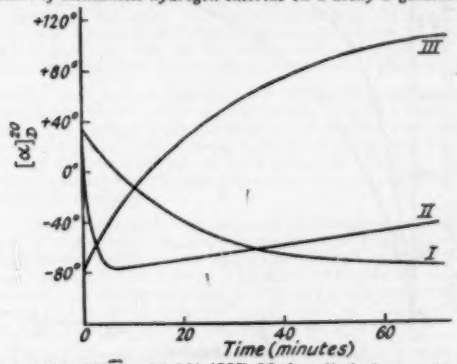
This paper describes the preparation of derivatives of this 2-deoxyhexose suitably protected so that phosphorylation will afford the required 2-deoxy-D-galactose-3 and -6 phosphoric acids.

D-Galactal prepared by the usual reactions, when dissolved in cold 5% sulphuric acid, yielded 2-deoxy-β-D-galactose. It has recently been shown that trifluoroacetic acid can successfully replace sulphuric acid in such reactions as aromatic nitration (Bourne, Stacey, Tatlow, and Tedder, unpublished results). It has now been shown that trifluoroacetic acid can also be used to convert D-galactal into 2-deoxy-β-D-galactose, the deoxy-sugar being characterised as its *p*-toluidine derivative. It was found that mutarotation of this compound occurred slowly when dry methanol and dry pyridine were used as solvents. Addition of one drop of 0·1N-sulphuric acid resulted in rapid attainment of the mutarotational equilibrium. The changes are shown in Fig. 1 (cf. Butler, Laland, Overend, and Stacey, *J.*, 1950, 1433, for analogous work with the 2-deoxy-D-galactose anilide). The deoxy-sugar also formed a crystalline diethyl and dibenzyl mercaptal. Treatment of 2-deoxy-D-galactose diethyl mercaptal with acetone in the presence of anhydrous zinc chloride, syrupy phosphoric acid, and phosphoric oxide, afforded 3 : 4-5 : 6-di*iso*propylidene 2-deoxy-D-galactose diethyl mercaptal.

The action of methanolic hydrogen chloride on a 2-deoxyhexose was first studied in detail by Hughes, Overend, and Stacey (*J.*, 1949, 2846). It was shown that treatment of 2-deoxy-D-glucose with methanolic hydrogen chloride resulted in a series of characteristic changes in the

FIG. 2.

Action of methanolic hydrogen chloride on 2-deoxy-D-galactose.



0·03% (I), 0·3% (II), and 3·0% (III) Methanolic hydrogen chloride.

optical rotation of the sugar. A similar series of changes has been revealed by the action of methanolic hydrogen chloride on 2-deoxy-D-galactose, but in this case the changes in optical rotation were found to be much greater than those observed with 2-deoxy-D-glucose. By using methanolic hydrogen chloride of various concentrations, a detailed examination of the whole range of changes in optical rotation was achieved (see Fig. 2). Treatment of 2-deoxy-D-galactose with 0·03% methanolic hydrogen chloride resulted in a decrease of the optical rotation to a minimum value of $-75° \pm 2°$. The difference between the initial and final (minimum) value was 112° (cf. 2-deoxy-D-glucose, for which the analogous figure was 4°). Termination of the reaction at the minimum value afforded a syrupy product which was shown by Overend, Shafizadeh, and Stacey (*J.*, 1950, 671) to be αβ-methyl-2-deoxy-D-galactofuranoside. When 2-deoxy-D-galactose was treated with 0·3% methanolic hydrogen chloride, the minimum value of the optical rotation was rapidly attained and was followed by a slow increase. When 3% methanolic hydrogen chloride was used, the minimum value of the optical rotation was attained instantaneously and was followed by a rapid increase to a maximum value of $125° \pm 2°$. Termination of the reaction at this stage afforded crystalline α-methyl-2-deoxy-D-galactopyranoside (cf. Overend, Shafizadeh, and Stacey, *loc. cit.*). Treatment of α-methyl-2-deoxy-D-galactoside with acetic anhydride and pyridine yielded syrupy 3 : 4 : 6-triacetyl α-methyl-2-deoxy-D-galactoside.

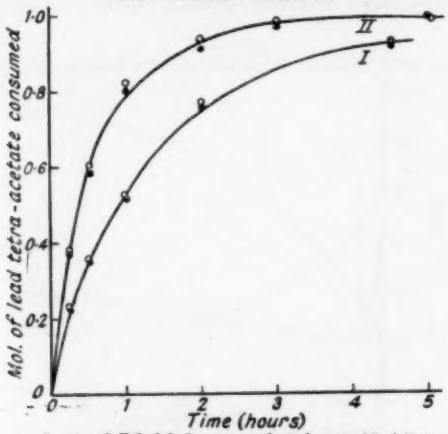
A series of changes similar to those described have been observed on treatment of 2-deoxy-D-galactose with ethanolic hydrogen chloride. Treatment of the deoxy-sugar with 2% ethanolic hydrogen chloride resulted in a rapid fall in the optical rotation to a minimum value

of $-56° \pm 2°$. Termination of the reaction at this stage yielded syrupy αβ-ethyl-2-deoxy-D-galactofuranoside. However, when the reaction was allowed to proceed until the optical rotation had reached a maximum value, the main product was αβ-ethyl-2-deoxy-D-galactopyranoside. A study of the rates of oxidation of these glycosides by lead tetra-acetate (see Fig. 3) confirmed that they had been correctly designated. Moreover, it was shown that, when D-galactal, which is known to have a pyranose structure, was treated with ethanolic hydrogen chloride, it afforded a glycoside identical in properties with that described above as αβ-ethyl-2-deoxy-D-galactopyranoside (cf. Overend, Shafizadeh, and Stacey, *loc. cit.*; Deriaz, Overend, Stacey, and Wiggins, *J.*, 1949, 2836).

When α-methyl-2-deoxy-D-galactoside was shaken with benzaldehyde containing anhydrous zinc chloride or heated in benzaldehyde at 145° in an atmosphere of carbon dioxide (Oldham and Honeyman, *J.*, 1946, 986), 4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside (Tamm and Reichstein, *Helv. Chim. Acta*, 1948, **31**, 1630) was obtained in 56·4% and 14% yield respectively. This on treatment with toluene-*p*-sulphonyl chloride in pyridine gave a monotoluene-*p*-sulphonyl derivative which did not react with sodium iodide in hot anhydrous acetone. It

FIG. 3.

Lead tetra-acetate oxidations.



I. ● αβ-*Ethyl-2-deoxy-*D-*galactofuranoside* (*A*).*
○ 1 : 2-iso*Propylidene* D-*glucofuranose*.
II. ● αβ-*Ethyl-2-deoxy-*D-*galactopyranoside* (*B*).*
○ α-*Methyl-2-deoxy-*D-*galactopyranoside*.

was 4 : 6-benzylidene 3-toluene-*p*-sulphonyl α-methyl-2-deoxy-D-galactoside since this failure to react confirmed that the toluene-*p*-sulphonyloxy-group was not located at position 6 of the sugar derivative. On treatment of α-methyl-2-deoxy-D-galactoside with acetone containing anhydrous zinc chloride 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galactoside was obtained. That the *iso*propylidene residue in this was located at $C_{(3)} : C_{(4)}$ was indicated by the fact that on treatment of the *iso*propylidene derivative with toluene-*p*-sulphonyl chloride in pyridine a crystalline monotoluene-*p*-sulphonyl derivative was obtained. This on treatment with sodium iodide in dry acetone under standard conditions underwent 36% exchange, thereby indicating that the toluene-*p*-sulphonyloxy-group was formed by reaction of the primary hydroxyl group in the sugar derivative (*i.e.*, that at $C_{(6)}$). Consequently the monotoluene-*p*-sulphonyl derivative was 3 : 4-*iso*propylidene 6-toluene-*p*-sulphony α-methyl-2-deoxy-D-galactoside. The incomplete exchange is in agreement with results previously reported (Foster, Overend, Stacey, and Wiggins, *J.*, 1949, 2542). Attempts to remove the *iso*propylidene residue by anhydrous methanolic hydrogen chloride or aqueous methanolic hydrochloric acid led to a crystalline substance which rapidly decomposed to a resinous material and could not be identified.

4 : 6-Benzylidene and 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galactoside were suitable intermediates for preparing 2-deoxy-D-galactose-3 and -6 phosphoric acid respectively (see following communication).

* For interpretation of (*A*) and (*B*) see p. 978.

Experimental.

2-Deoxy-β-D-galactose.—(a) *By the action of sulphuric acid on D-galactal.* D-Galactal (30 g.) was dissolved in cold 5% sulphuric acid (400 c.c.), and the solution was kept at 0° for 24 hours, and then adjusted to pH 7 by addition of aqueous barium hydroxide. The barium residues were collected by filtration and well washed with water. The washings were added to the filtrate which was then evaporated under diminished pressure to a syrup. Methanol was distilled over the syrup several times to remove traces of water. The pale yellow syrup which was finally obtained was dissolved in dry methanol (50 c.c.), filtered through a carbon pad, and set aside. 2-Deoxy-β-D-galactose (14 g.) crystallised readily and a further crop of crystals (4 g.) was obtained after concentration of the mother-liquors. The deoxyhexose had m. p. 120—121°, and $[\alpha]_D^{20}$ +8° changing to +38° ± 2° after 70 minutes (*c*, 2·0 in methanol), and +24° changing to +56° ± 2° after 120 minutes (*c*, 2·0 in water). Pigman and Isbell (*J. Res. Nat. Bur. Stand.*, 1937, **19**, 189; 1939, **22**, 397) give m. p. 120—121°, and $[\alpha]_D^{20}$ +40·8° changing to +60·5° after 30 minutes in water; Overend, Shafizadeh, and Stacey (*J.*, 1950, 671) report $[\alpha]_D^{17}$ +33·6° after 2 minutes, changing to +57° after 46 minutes in water, and Tamm and Reichstein (*Helv. Chim. Acta*, 1948, **31**, 1630) quote $[\alpha]_D^{18}$ +60·7° in water.

(b) *By the action of trifluoracetic acid on D-galactal.* D-Galactal (1·0 g.) was dissolved in water (13 c.c.) at 0° containing trifluoroacetic acid (1·0 g.), and the solution was set aside at 0° for 48 hours. The green and slightly turbid solution was filtered through a charcoal pad and evaporated in the frozen state. The syrupy residue was dissolved in the minimum volume of water, and adjusted to pH 7 by the addition of sodium carbonate. After being shaken with charcoal the solution was evaporated to a syrup and then crystallised as in (a) above. 2-Deoxy-β-D-galactose (0·52 g.; m. p. 120—121°) was obtained.

2-Deoxy-D-galactose p-Toluidide.—A solution of 2-deoxy-β-D-galactose (0·3 g.) in 95% ethanol (7 c.c.) was boiled under reflux with *p*-toluidine (0·23 g., 1·1 mols.) for 2 hours. After 24 hours at 0° crystals had separated and were collected. After recrystallisation from ethanol, 2-deoxy-D-galactose *p*-toluidide (0·25 g., 54%) was obtained as large colourless prisms, m. p. 142—143°, $[\alpha]_D^{20}$ −148·9° (*c*, 0·8 in pyridine) (Found: C, 61·9; H, 7·6; N, 5·2. Calc. for $C_{13}H_{19}O_4N$: C, 61·7; H, 7·5; N, 5·5%). 2-Deoxy-D-galactose *p*-toluidide showed mutarotation in methanol and pyridine.

(*a*) Pyridine as solvent: The optical rotation of a 1% solution of the toluidide in dry pyridine changed from −150° after 1 minute to −115° after 72 hours. When 1 drop of 0·1N-sulphuric acid was added to a similar solution, the changes observed were −127·5° after 1 minute, altering to −110° after 9 minutes. (*b*) Methanol as solvent: The optical rotation of a 1% solution of the *p*-toluidide in dry methanol changed from −117° after 1 minute to −65° after 100 minutes. If 1 drop of 0·1N-sulphuric acid was added to a similar solution the changes observed in optical rotation were −115° (extrapolated initial value) to −62·5° after 3 minutes.

2-Deoxy-D-galactose Dibenzyl Mercaptal.—A solution of 2-deoxy-β-D-galactose (0·75 g.) in concentrated hydrochloric acid (1·5 c.c.) was shaken vigorously with toluene-α-thiol (2·6 mols., 1·3 c.c.). Treatment of the reaction mixture with ice and water gave a thick semi-solid mass which collapsed to a flocculent precipitate on treatment with ether. The solid was collected and washed alternately with water and ether. Recrystallisation from aqueous methanol gave *2-deoxy-D-galactose dibenzyl mercaptal* (0·8 g., 44%) as glistening plates, m. p. 106—107°, $[\alpha]_D^{20}$ −38° (*c*, 1·72 in pyridine) (Found: C, 61·2; H, 6·5; S, 15·6. $C_{20}H_{24}O_4S_2$ requires C, 60·9; H, 6·6; S, 16·2%).

2-Deoxy-D-galactose Diethyl Mercaptal.—On shaking of a solution of 2-deoxy-β-D-galactose (3 g.) in concentrated hydrochloric acid (6 c.c.) with ethanethiol (4·5 c.c.) for 2 hours at room temperature and then pouring of the reaction mixture into water, 2-deoxy-D-galactose diethyl mercaptal (4·3 g., 87%) was obtained. After recrystallisation from aqueous methanol the mercaptal showed m. p. 104—105° and $[\alpha]_D^{20}$ −45° (*c*, 1·0 in ethanol). Overend, Shafizadeh, and Stacey (*loc. cit.*) record m. p. 104—105° for this compound.

3 : 4-5 : 6-Diisopropylidene 2-Deoxy-D-galactose Diethyl Mercaptal.—The diethyl mercaptal (4·2 g.) was shaken in dry acetone (150 c.c.) containing anhydrous zinc chloride (4 g.), phosphoric oxide (3 g.), and syrupy phosphoric acid (5 c.c.) at room temperature for 50 hours. The solution was poured into water containing an excess of sodium carbonate. The precipitated zinc salts were collected and well washed with acetone. The washings were added to the filtrate, which was then evaporated under diminished pressure to remove the acetone. The aqueous residue was extracted with chloroform (5 × 100 c.c.), the extract dried ($MgSO_4$), and the solvent removed by evaporation. Distillation of the syrupy residue afforded *3 : 4-5 : 6-diisopropylidene 2-deoxy-D-galactose diethyl mercaptal* (3·5 g., 65%), b. p. 145—155° (bath-temp.)/0·05 mm., n_D^{20} 1·4835, $[\alpha]_D^{20}$ +13·9° (*c*, 0·8 in acetone) (Found: C, 54·0; H, 8·2. $C_{14}H_{26}O_4S_2$ requires C, 54·8; H, 8·6%).

Treatment of 2-Deoxy-D-galactose Diethyl Mercaptal with Benzaldehyde.—(a) *In the presence of zinc chloride.* 2-Deoxy-D-galactose diethyl mercaptal (0·2 g.) was shaken with freshly distilled benzaldehyde (2 c.c.) and finally powdered anhydrous zinc chloride (1 g.). The mixture rapidly became deep red in colour and after 48 hours was treated with a mixture of water and light petroleum (b. p. 60—80°). No crystalline products could be isolated.

(b) *At elevated temperatures* (cf. Oldham and Honeyman, *J.*, 1946, 986). A mixture of freshly distilled benzaldehyde (3 c.c.) and 2-deoxy-D-galactose diethyl mercaptal (8 c.c.) was heated at 140—145° for 2 hours. A rapid stream of carbon dioxide was passed through the reaction mixture during this period. Working up in the usual manner gave no crystalline product.

Action of Methanolic Hydrogen Chloride on 2-Deoxy-β-D-galactose.—(a) *0·03% Methanolic hydrogen chloride.* 2-Deoxy-β-D-galactose (0·1 g.) dissolved in dry methanol (9 c.c.) was allowed to mutarotate

to equilibrium (40 minutes). 0·3% Methanolic hydrogen chloride (1 c.c.) was added and the change in optical rotation observed :

Time (mins.)	4	8	13	19	30	40	70	90
$[\alpha]_D^{18}$	+17°	−3°	−21°	−37°	−52°	−63°	−73°	−75°

Neutralisation of the acid with excess silver carbonate after 90 minutes followed by removal of the silver residues and evaporation of the solvent gave a syrup which did not reduce Fehling's solution. It was αβ-methyl-2-deoxy-D-galactofuranoside (cf. Overend, Shafizadeh, and Stacey, *loc. cit.*).

(b) 0·3% *Methanolic hydrogen chloride.* 3% Methanolic hydrogen chloride (1 c.c.) was added to a solution of 2-deoxy-β-D-galactose (0·1 g.) in dry methanol (9 c.c.), which had mutarotated to equilibrium. The changes observed in the optical rotation were as follows :

Time (mins.)	1	1·5	2·5	5	16	28	41	55	71
$[\alpha]_D^{18}$	−50°	−60°	−70°	−75°	−70°	−65°	−57°	−49°	−40°

(c) 3·0% *Methanolic hydrogen chloride.* Addition of 30% methanolic hydrogen chloride (1 c.c.) to a solution of 2-deoxy-β-D-galactose in methanol, identical with that previously described, resulted in the following changes in optical rotation :

Time (mins.)	0·5	1	5	11	16	25	40	90	200
$[\alpha]_D^{20}$	−77°	−60°	−43°	−14°	+11°	+43°	+74°	+106°	+114°

Neutralisation of the solution at the maximum value of the optical rotation and isolatio of the product in the usual manner afforded α-methyl-2-deoxy-D-galactopyranoside, m. p. 112—113° after recrystallisation from ethyl acetate), $[\alpha]_D^{20}$ +155° (*c*, 1·0 in water). Overend, Shafizadeh, and Stacey (*loc. cit.*) cite m. p. 112—113° for this compound, and Tamm and Reichstein (*loc. cit.*) give m. p. 109—110°.

3 : 4 : 6-*Triacetyl α-Methyl-2-deoxy-D-galactoside.*—α-Methyl-2-deoxy-D-galactoside (0·5 g.) in solution in dry pyridine (4 c.c.) was treated with excess of acetic anhydride for 4 days at room temperature. The reaction mixture was diluted with water (150 c.c.) and extracted with chloroform (3 × 50 c.c.). The extract was washed successively with water, dilute aqueous sodium hydrogen carbonate, and again with water. After drying ($MgSO_4$) the solution was evaporated and afforded a straw-coloured syrup. On distillation 3 : 4 : 6-*triacetyl α-methyl-2-deoxy-D-galactoside* was obtained as a colourless syrup, b. p. 125—130° (bath-temp.)/0·03 mm., n_D^{20} 1·4504, $[\alpha]_D^{20}$ +159° (*c*, 1·0 in benzene) (Found : C, 52·0; H, 7·2. $C_{13}H_{20}O_8$ requires C, 51·3; H, 6·7%).

Action of Ethanolic Hydrogen Chloride on 2-Deoxy-β-D-galactose.—(a) 0·8% *Ethanolic hydrogen chloride.* 2-Deoxy-β-D-galactose (0·1 g.) was dissolved in dry ethanol (5 c.c.) and allowed to mutarotate to equilibrium (40 minutes). 20·8% Ethanolic hydrogen chloride (0·2 c.c.) was then added and the changes in optical rotation of the solution were observed :

Time (mins.)	0	1	2	3	5	10	30
$[\alpha]_D^{18}$	+23°	−28°	−51°	−55°	−56°	−52°	−38°

In a parallel experiment the solution was neutralised after 5 minutes (*i.e.*, minimum value of the optical rotation) with excess of silver carbonate. Removal of the silver residues and evaporation of the solvent gave *αβ-ethyl-2-deoxy-D-galactofuranoside* (*A*) as a colourless syrup, $[\alpha]_D^{20}$ −56° in ethanol (Found : OEt, 23·0. $C_8H_{16}O_5$ requires OEt, 23·4%).

(b) 2·3% *Ethanolic hydrogen chloride.* A solution of 2-deoxy-β-D-galactose similar to that described above was treated with 20% ethanolic hydrogen chloride (0·7 c.c.), and the changes in optical rotation were observed polarimetrically :

Time (mins.)	0	1	2	6	12	27	43	800
$[\alpha]_D^{18}$	+22°	−46°	−42°	−30°	−10°	+24°	+42°	+101°

After 800 minutes the solution was neutralised and the product isolated in the usual manner. *αβ-Ethyl-2-deoxy-D-galactopyranoside* (*B*) was obtained, having $[\alpha]_D^{20}$ +110° in ethanol (Found : OEt, 22·9%).

Oxidation of (*A*) *and* (*B*) *with Lead Tetra-acetate.*—The oxidations were carried out according to the procedure of Hockett and McClenahan (*J. Amer. Chem. Soc.*, 1939, **61**, 1667) (cf. Overend, Shafizadeh, and Stacey, *loc. cit.*, for analogous experiments with the corresponding methylglycosides of 2-deoxy-D-galactose). The results obtained were as follows :

(*a*) αβ-Ethyl 2-deoxy-D-galactofuranoside (96 mg.)

Time (hours)	0·25	0·5	1·0	2·0	4·5	80
Mols. of $Pb(OAc)_4$ used	0·23	0·35	0·52	0·77	0·93	0·97

(*b*) αβ-Ethyl 2-deoxy-D-galactopyranoside (95 mg.)

Time (hours)	0·25	0·5	1·0	2·0	3·0	5·0
Mols. of $Pb(OAc)_4$ used	0·38	0·59	0·81	0·92	0·98	1·04

For purposes of comparison, a similar experiment was carried out on equimolecular amounts of 1 : 2-*iso*propylidene D-glucofuranose and α-methyl-2-deoxy-D-galactoside.

(*c*) 1 : 2-isoPropylidene D-glucofuranose (110 mg.)

Time (hours)	0·25	0·5	1·0	2·0	2·5	4·5	8·0	15
Mols. of $Pb(OAc)_4$ used	0·25	0·36	0·53	0·79	0·84	0·96	0·98	1·01

(*d*) α-Methyl 2-deoxy-D-galactoside (92 mg.)

Time (hours)	0·25	0·5	1·0	2·0	3·0	5·0
Mols. of $Pb(OAc)_4$ used	0·39	0·61	0·83	0·94	1·0	1·07

Reaction of D-*Galactal with Hydrogen Chloride in Primary Alcohols.*—(a) 0·4% *Methanolic hydrogen chloride.* D-Galactal (0·1 g.) was dissolved in dry methanol (5 c.c.) ($[\alpha]_D^{20}$ of this solution was −29°), and 2·6% methanolic hydrogen chloride (1 c.c.) was added. The following changes in the optical rotation of the solution were observed polarimetrically :

Time (mins.)	1	2	3	5	9	14	20	43
$[\alpha]_D^{20}$	+6°	+58°	+80°	+102°	+116°	+122°	+125°	+127°

Neutralisation of the solution with silver carbonate and isolation of the product in the usual manner afforded α-methyl-2-deoxy-D-galactoside (60%), m. p. 112—113° alone or on admixture with the sample previously described.

(b) 0·8% *Ethanolic hydrogen chloride.* To a solution of D-galactal (0·1 g.) in ethanol (5 c.c.) ($[\alpha]_D^{20}$ −38° for this solution), 20% ethanolic hydrogen chloride (0·2 c.c.) was added and the changes in optical rotation were observed polarimetrically :

Time (mins.)	1	2	4	6	8	15	30	50
$[\alpha]_D^{20}$	+16°	+48°	+79°	+94°	+101°	+111°	+113°	+114°

Neutralisation of the solution and isolation of the product in the usual manner afforded αβ-ethyl-2-deoxy-D-galactopyranoside, $[\alpha]_D^{20}$ +114° in ethanol (Found : OEt, 22·9%).

4 : 6-*Benzylidene* α-*Methyl-2-deoxy-*D-*galactoside.*—(*a*) α-Methyl-2-deoxy-D-galactoside (4·7 g.) was shaken with freshly distilled benzaldehyde (15 c.c.) until dissolution was essentially complete. Finely powdered anhydrous zinc chloride (6 g.) was then added and the mixture was mechanically agitated for 3 days at room temperature. Addition of the mixture to water and light petroleum (b. p. 60—80°) afforded a crystalline solid. This was separated and dissolved in chloroform, and the solution washed successively with water, dilute aqueous sodium hydroxide solution, and again with water. After drying ($MgSO_4$) the solvent was removed by evaporation and the crystalline residue recrystallised from aqueous methanol. 4 : 6-Benzylidene α-methyl-2-deoxy-D-galactoside (3·95 g., 56%) was obtained as colourless needles, m. p. 178—179°, $[\alpha]_D^{20}$ +106° (*c*, 0·62 in chloroform) (Found : C, 63·0; H, 6·6. $C_{14}H_{18}O_5$ requires C, 63·2; H, 6·8%) [Tamm and Reichstein, *loc. cit.* who described this compound after the completion of this work give m. p. 179—180° and $[\alpha]_D^{18}$ +108·4° ±3° (in chloroform)].

(*b*) (cf. Oldham and Honeyman, *loc. cit.*). α-Methyl-2-deoxy-D-galactoside (2·5 g.) and benzaldehyde (15 c.c.) were heated together at 140—145° for 2 hours, during which a stream of carbon dioxide was bubbled through the reaction mixture. After cooling, light petroleum (b. p. 60—80°) was added and unchanged material and its benzylidene derivative were separated as a semi-solid mass. After trituration with more light petroleum (b. p. 60—80°) this was dissolved in chloroform, and the product (0·5 g.) was isolated as described above, m. p. 178—179°.

4 : 6-*Benzylidene* 3-*Toluene-*p*-sulphonyl* α-*Methyl-2-deoxy-*D-*galactoside.*—The benzylidene derivative (0·5 g.) was dissolved in dry pyridine (2 c.c.), and toluene-*p*-sulphonyl chloride (1·2 mols., 1·4 g.) was added. After 1 day at room temperature the reaction mixture was poured into water. The solid product was filtered off and recrystallised from ethanol. The toluene-*p*-sulphonyl derivative was obtained as colourless, lustrous plates, m. p. 134—135°, $[\alpha]_D^{20}$ +154·3° (*c*, 1·1 in chloroform) (Found : C, 59·8; H, 6·2. Calc. for $C_{21}H_{24}O_7S$: C, 60·0; H, 5·7%). The yield was quantitative (cf. Tamm and Reichstein, *loc. cit.*, who give m. p. 125—129° for this compound). When this compound (0·2 g.) was heated at 110—115° for 5 hours with excess of dry sodium iodide (0·5 g.) in dry acetone solution (5 c.c.), no reaction occurred and the starting materials could be recovered unchanged.

3 : 4-iso*Propylidene* α-*Methyl-2-deoxy-*D-*galactoside.*—α-Methyl-2-deoxy-D-galactoside (2·3 g.) was shaken with dry acetone (50 c.c.) containing anhydrous zinc chloride (6 g.) at room temperature for 40 hours. The mixture was then poured into water (250 c.c.) containing an excess of sodium carbonate, and the precipitate was collected and washed with acetone. The washings were added to the filtrate which was evaporated under diminished pressure to small bulk. The aqueous residue was extracted exhaustively with chloroform, the extract was dried ($MgSO_4$), and the solvent evaporated. 3 : 4-iso-*Propylidene* α-*methyl-2-deoxy-*D-*galactoside* (1·0 g.) was obtained as a straw-coloured syrup, n_D^{20} 1·4660, $[\alpha]_D^{20}$ +92·5° (*c*, 1·04 in acetone) (Found : C, 54·8; H, 8·3. $C_{10}H_{18}O_5$ requires C, 55·0; H, 8·3%).

3 : 4-iso*Propylidene* 6-*Toluene-*p*-sulphonyl* α-*Methyl-2-deoxy-*D-*galactoside.*—The *iso*propylidene derivative (0·66 g.) was dissolved in dry pyridine (4 c.c.), and toluene-*p*-sulphonyl chloride (0·7 g.) was added. After 20 hours at room temperature the product was isolated in the usual manner. After recrystallisation from aqueous ethanol, 3 : 4-iso*propylidene* 6-*toluene-*p*-sulphonyl* α-*methyl-2-deoxy-*D-*galactoside* (0·7 g.) was obtained as colourless prisms, m. p. 92—93°, $[\alpha]_D^{20}$ +44° (*c*, 0·91 in acetone) (Found : C, 54·9; H, 6·5; S, 8·7. $C_{17}H_{24}O_7S$ requires C, 54·8; H, 6·5; S, 8·6%). This compound (0·4 g.) was treated with anhydrous sodium iodide (0·19 g.) in dry acetone (10 c.c.) at 140° for 5 hours. Sodium toluene-*p*-sulphonate (82 mg.) was precipitated, corresponding to 36% of that required for complete exchange (cf. Foster *et al.*, *loc. cit.*).

One of us (A. B. F.) thanks the Brewing Industry Research Foundation for financial assistance and we acknowledge the award of a grant for technical assistance by the British Rubber Producers' Research Association.

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[*Received, November 29th,* 1950.]

219. *Deoxy-sugars. Part XV.* D-*Galactose-3 and -6 Phosphoric Acids and Their 2-Deoxy-analogues.*

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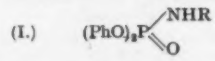
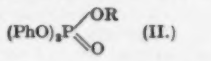
Syntheses of D-galactose-3 and -6 phosphoric acids and their 2-deoxy-analogues are described. Structures of intermediates are established. The phosporylating agent used, namely diphenyl phosphoryl chloride, has been characterised by reaction with ammonia, aliphatic and aromatic amines, alcohols, and phenols.

In the past a variety of reagents has been used for the phosphorylation of sugars, but many of these were extremely drastic in their action. Because of the lability and scarcity of most deoxy-sugars, many of these reagents were of little value for the preparation of deoxy-sugar phosphates. To synthesise 2-deoxy-D-galactose-3 and -6 phosphoric acids, two phosphorylating agents have been used, namely, phosphorus oxychloride in pyridine at −40° (Levene, *J. Biol. Chem.*, 1934, **106**, 113; 1935, **111**, 313; 1937, **121**, 131), and diphenyl phosphoryl chloride (diphenyl chlorophosphonate), $(PhO)_2POCl$, in pyridine at 0°. The former method, where successful, has the advantage of direct introduction into the sugar derivative of a free phosphate group in good yield, but does not readily afford crystalline compounds. The latter has been used by several workers (Gulland and Hobday, *J.*, 1940, 746; Brigl and Müller, *Ber.*, 1939, **72**, 2121; Bredereck *et al.*, *Ber.*, 1940, **73**, 269, 1124; Zeile and Meyer, *Z. physiol. Chem.*, 1938, **256**, 131; Baer and Fischer, *J. Biol. Chem.*, 1943, **150**, 213, 223; Baer and MacArther, *ibid.*, 1944, **153**, 451; Farrar, *J.*, 1949, 3131) but has never been systematically investigated. Diphenyl phosphoryl chloride has the advantages of being easily prepared and stored, and affords crystalline derivatives (Farrar, *loc. cit.*). It was prepared by a modification of Brigl and Müller's method (*loc. cit.*). Treatment of phenol with phosphorus oxychloride at 200° gave a mixture of three esters, namely, phenyl phosphoryl dichloride ($PhO{\cdot}POCl_2$), diphenyl phosphoryl chloride, and triphenyl phosphate. These were readily fractionated and diphenyl phosphoryl chloride isolated as a pungent colourless liquid. It reacts readily with both aliphatic and aromatic amines, although more smoothly with the former. For example, treatment of diphenyl phosphoryl chloride, in carbon tetrachloride at 0°, with gaseous ammonia gave diphenyl aminophosphonate (I; R = H). Replacement of ammonia by a primary amine such as *cyclo*hexylamine in carbon tetrachloride solution, or benzylamine,



(I.)



(II.)

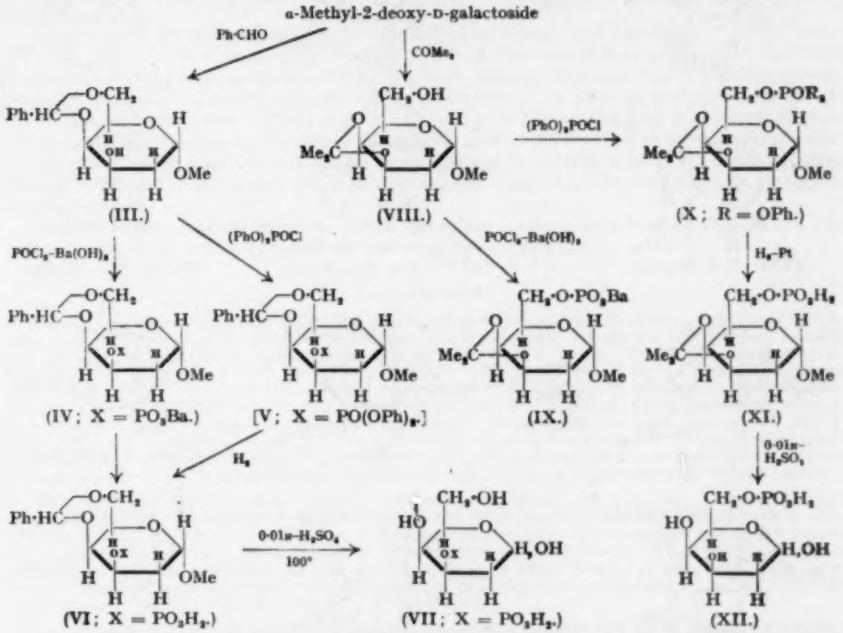
afforded diphenyl *cyclo*hexylaminophosphonate (I; R = C_6H_{11}) and diphenyl benzylamino-phosphonate (I; R = $C_6H_5{\cdot}CH_2$) respectively. The secondary amine, morpholine, readily yielded diphenyl morpholinophosphonate (I; R = $O<[CH_2{\cdot}CH_2]_2>N-$. A solution of aniline in carbon tetrachloride with diphenyl phosphoryl chloride gave diphenyl anilino-phosphonate (I; R = Ph), and diphenyl phenetidinophosphonate (I; R = p-$EtO{\cdot}C_6H_4$) and diphenyl phenylazoanilinophosphonate (I; R = $PhN{:}N{\cdot}C_6H_4$) were similarly prepared. The aminophosphonate derivatives were highly crystalline and well suited for the characterisation of diphenyl phosphoryl chloride.

Similarly diphenyl phosphoryl chloride reacts with aliphatic alcohols and phenols, most easily in the aliphatic series. *cyclo*Hexanol in solution in dry pyridine readily gave *cyclo*hexyl diphenyl phosphate (II; R = C_6H_{11}). Surprisingly, no crystalline products could be isolated from the reaction between diphenyl phosphoryl chloride and furfuryl alcohol or benzyl alcohol. Phenol gave triphenyl phosphate (II; R = Ph) identical with that isolated by Jacobsen (*Ber.*, 1875, **8**, 1522) after direct reaction of phenol and phosphorus oxychloride at 200°. Similarly β-naphthyl diphenyl phosphate (II; R = $C_{10}H_7$) and p-nitrophenyl diphenyl phosphate (II; R′ = p-$C_6H_4{\cdot}NO_2$) were prepared. The compounds obtained by treating diphenyl phosphoryl chloride with alcohols and phenols were not so characteristically crystalline as those obtained from amines, generally being viscid liquids or low-melting solids.

When 4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside (III) (see preceding paper) was treated with phosphorus oxychloride in pyridine at −40°, followed by barium hydroxide, it gave amorphous barium 4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside-3 phosphate (IV).

Treatment of (III) with diphenyl phosphoryl chloride in pyridine gave crystalline (4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside-3) diphenyl phosphate (V).

Before hydrogenolysis of this substance a solution in methanol of 4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside (III) was shown to be unchanged when shaken with Adams's catalyst in an atmosphere of hydrogen. Using a Raney nickel catalyst Tamm and Reichstein (*Helv. Chim. Acta*, **1948**, **31**, 1630) succeeded in saturating the benzylidene substituent by shaking (III) in hydrogen under pressure and they isolated 4 : 6-hexahydrobenzylidene α-methyl-2-deoxy-D-galactoside; they did not observe any cleavage of the benzylidene residue under the conditions

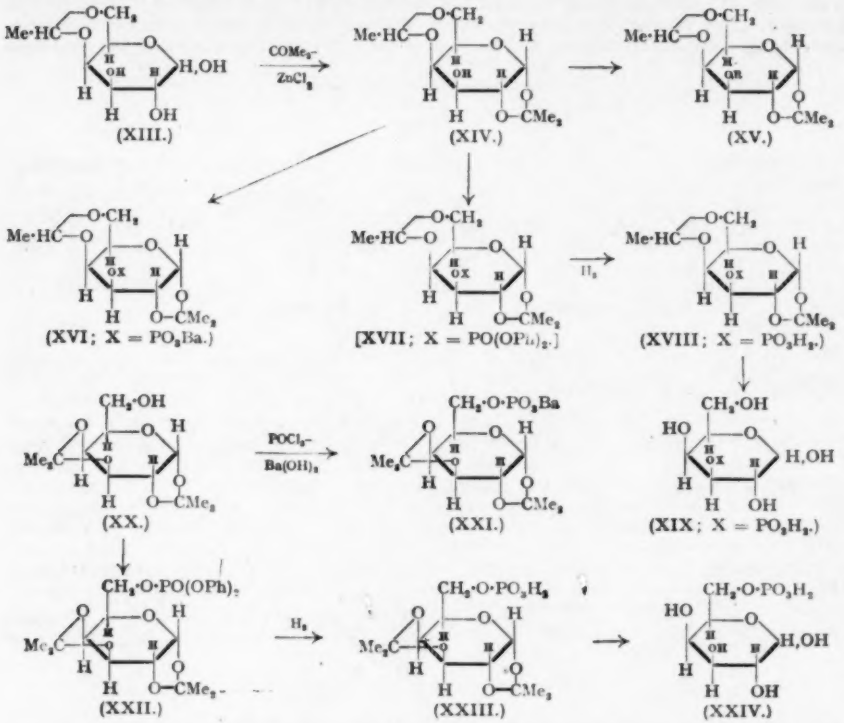


used. When (4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside-3) diphenyl phosphate (V) was subjected to hydrogenation in the presence of platinum oxide as already described, hydrogen was rapidly absorbed, corresponding to both cleavage and saturation of the phenyl groups, and it was possible to isolate 4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside-3 phosphoric acid (VI) as a colourless hygroscopic glass, which on treatment with a methanolic solution of acridine afforded a crystalline acridine salt. Treatment of (VI) with 2N-sulphuric acid under conditions identical with those which effected hydrolysis of α-methyl-2-deoxy-D-galactoside resulted in an extremely slow reaction, but at 45° there was smooth hydrolysis of the protecting groups. Unfortunately simultaneous hydrolysis of the phosphate residue also occurred. However, if a solution of (VI) in 0·01N-sulphuric acid was heated at 100° for 13 minutes, hydrolysis of the protecting groups was smooth and 2-deoxy-D-galactose-3 phosphoric acid was then isolated as its lead salt. Decomposition of the lead salt with hydrogen sulphide gave 2-deoxy-D-galactose-3 phosphoric acid (VII) as an amorphous white powder.

For the synthesis of 2-deoxy-D-galactose-6 phosphoric acid (XII), syrupy 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galactoside (VIII) (see preceding paper) was treated with phosphorus oxychloride in pyridine at −40°, followed by barium hydroxide. Barium 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galactoside-3 phosphate (IX) was obtained as an amorphous powder.

Treatment of (VIII) with diphenyl phosphoryl chloride in pyridine at 0° gave syrupy diphenyl (3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galactoside-6) phosphate (X). A solution of this in aqueous ethanol, after removal of catalyst poisons by boiling under reflux with activated charcoal, absorbed hydrogen (8 mols.) in presence of platinum oxide. As before, this

corresponded to both saturation and cleavage of the phenyl groups and the formation of 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galactoside-6 phosphoric acid (XI). No crystalline acridine salt of this compound has been obtained. Hydrolysis of (XI) with 0·01N-sulphuric acid at 100° for 30 minutes gave 2-deoxy-D-galactose-6 phosphoric acid (XII) as a fine white powder, strongly reducing towards Fehling's reagent.



For comparison of their properties (see following paper), D-galactose-3 and -6 phosphoric acids were also synthesised. Treatment of D-galactose with paraldehyde and concentrated sulphuric acid afforded a liquid ethylidene galactose. That this was 4 : 6-ethylidene D-galactose (XIII) was indicated by several facts. For example, it was strongly reducing towards Fehling's solution, indicating that $C_{(1)}$ of the sugar was not involved in the ethylidene linkage. Reaction with acetone and anhydrous zinc chloride afforded a syrupy compound (*A*), which was non-reducing and was subsequently shown to be 4 : 6-ethylidene 1 : 2-*iso*propylidene D-galactose.

Treatment of (*A*) with toluene-*p*-sulphonyl chloride in pyridine yielded crystalline ethylidene *iso*propylidene toluene-*p*-sulphonyl D-galactose, which when heated under standard conditions with sodium iodide in acetone underwent no reaction, showing that the toluene-*p*-sulphonyloxy-group was unlikely to be located at $C_{(6)}$ in galactose. Clearly the ethylidene residue was linked across positions 4 : 6 or 3 : 6. Normally the latter linkage is not formed if the former can take place, and so the ethylidene derivative is considered to be 4 : 6-ethylidene D-galactose (XIII). (*A*) would be 4 : 6-ethylidene 1 : 2-*iso*propylidene D-galactose (XIV), and its toluene-*p*-sulphonyl derivative, 4 : 6-ethylidene 1 : 2-*iso*propylidene 3-toluene-*p*-sulphonyl D-galactose (XV; R = ·SO_2·C_6H_4Me). The corresponding 3-methanesulphonyl derivative (XV; R = ·SO_2·Me) was obtained as a crystalline solid; this did not react with sodium iodide in dry acetone under standard conditions.

When 4 : 6-ethylidene 1 : 2-*iso*propylidene D-galactose (XIV) was treated with phosphorus oxychloride in pyridine at −40°, followed by barium hydroxide, barium 4 : 6-ethylidene 1 : 2-

*iso*propylidene D-galactose-3 phosphate (XVI) was obtained as an amorphous powder. Reaction of (XIV) with diphenyl phosphoryl chloride in pyridine solution at 0° gave syrupy (4 : 6-ethylidene 1 : 2-*iso*propylidene D-galactose-3) diphenyl phosphate (XVII) which, after removal of catalyst poisons in the manner already described, absorbed hydrogen (8·2 mols.) when in the presence of platinum oxide. 4 : 6-Ethylidene 1 : 2-*iso*propylidene D-galactose-3 phosphoric acid (XVIII) was isolated as a hygroscopic glass which readily gave a crystalline acridine salt. A dilute aqueous solution of this salt exhibited a characteristic green fluorescence. Treatment of (XVIII) with 0·01N-sulphuric acid at 100° for 1 hour afforded D-galactose-3 phosphoric acid (XIX) (42%) as a colourless glass which could be converted into a crystalline dipotassium or acridine salt.

D-Galactose-6 phosphoric acid was first described by Levene and Raymond (*J. Biol. Chem.*, 1931, **92**, 765). It was prepared by treating 1 : 2-3 : 4-di*iso*propylidene D-galactose (XX) with phosphorus oxychloride as already described, and then hydrolysing the protecting groups. Diphenyl phosphoryl chloride converted (XX) into syrupy (1 : 2-3 : 4-di*iso*propylidene D-galactose-6) diphenyl phosphate (XXII) from which 1 : 2-3 : 4-di*iso*propylidene D-galactose-6 phosphoric acid (XXIII) and D-galactose-6 phosphoric acid (XXIV) were obtained by successive hydrogenation in the presence of Adams's catalyst and hydrolysis with 0·01N-sulphuric acid. Both (XXIII) and (XXIV) were obtained as colourless glasses, but the former gave a crystalline acridine salt.

The properties and stabilities of these phosphoric acid derivatives of D-galactose and 2-deoxy-D-galactose are described in the following communication.

Experimental.

Diphenyl Phosphoryl Chloride.—Freshly distilled phosphorus oxychloride (150 g.) and phenol (200 g.) were mixed. A vigorous evolution of hydrogen chloride occurred. When the reaction had subsided the mixture was gradually heated and kept at 200° for 4 hours. Distillation then afforded fractions: (i) (112 g.), b. p. 105—110°/12—15 mm., n^{15} 1·5318 (this was phenyl phosphoryl dichloride, (PhO·POCl$_2$); (ii) (75 g.), b. p. 180—190°/12—15 mm., n^{15} 1·5505 (diphenyl phosphoryl chloride); and (iii) (75 g.), b. p. 210—250°/12—15 mm. (triphenyl phosphate). Fraction (iii) was obtained originally as a colourless viscous liquid, but crystallised on storage. Recrystallisation from ether gave a product of m. p. 41—43° (Jacobsen, *loc. cit.*, gives m. p. 41—43°). The diphenyl phosphoryl chloride (fraction ii) was re-distilled twice and obtained as a colourless liquid with a characteristic pungent odour. It could be conveniently stored in the presence of phosphoric oxide, but in sunlight gradually became yellow.

Reaction of Diphenyl Phosphoryl Chloride with Amino-compounds.—(a) *Ammonia.* A rapid stream of ammonia was bubbled through a solution of diphenyl phosphoryl chloride (1·73 g.) in carbon tetrachloride (10 c.c.) cooled to −10°. After 5 minutes, when reaction was complete, excess of ammonia was removed by passing a rapid stream of nitrogen through the mixture. The crystalline material formed was collected and freed from inorganic material by being washed several times with water. Recrystallisation from aqueous methanol afforded diphenyl aminophosphonate, m. p. 148—149° (Atherton and Todd, *J.*, 1947, 674, record m. p. 149—150°).

(b) *Aliphatic amines.* A solution of diphenyl phosphoryl chloride (1·0 g.) in carbon tetrachloride (10 c.c.) was treated at room temperature with a solution of freshly distilled *cyclo*hexylamine (1·0 g.) in carbon tetrachloride (10 c.c.), and the reaction mixture was set aside overnight. After dilution with carbon tetrachloride (40 c.c.) the solution was washed successively with water, dilute hydrochloric acid, and again water. After drying ($MgSO_4$), evaporation of solvent afforded a crystalline residue. Recrystallization from aqueous methanol gave *diphenyl* cyclo*hexylaminophosphonate* as colourless needles, m. p. 101—102° (Found: C, 65·3; H, 6·6; N, 4·1. $C_{18}H_{22}O_3NP$ requires C, 65·2; H, 6·6; N, 4·2%). By similar methods, using benzylamine and morpholine, were prepared *diphenyl benzylamino-phosphonate*, large colourless needles (from aqueous methanol), m. p. 103—104° (Found: C, 67·2; H, 5·2. $C_{19}H_{18}O_3NP$ requires C, 67·2; H, 5·3%), and *diphenyl morpholinophosphonate*, colourless plates (from aqueous methanol), m. p. 71—72° (Found: 60·3; H, 5·6; N, 4·5. $C_{16}H_{18}O_4NP$ requires C, 60·2; H, 5·6; N, 4·4%).

(c) *Aromatic amines.* A solution of freshly distilled aniline (0·5 g.) in carbon tetrachloride (5 c.c.) was added to a solution of diphenyl phosphoryl chloride (0·5 g.) in the same solvent (10 c.c.). The solution was set aside at room temperature overnight, and then worked up in the usual manner. Recrystallisation of the product from aqueous methanol afforded *diphenyl anilinophosphonate* as colourless plates, m. p. 128—129° (Found: C, 65·8; H, 5·0. $C_{18}H_{16}O_3NP$ requires C, 66·5; H, 4·9%).

By similar methods were prepared *diphenyl phenetidinophosphonate*, colourless hexagonal plates (from aqueous methanol), m. p. 104—105° (Found: C, 65·3; H, 5·4. $C_{20}H_{20}O_4NP$ requires C, 65·1; H, 5·4%), and *diphenyl phenylazoanilinophosphonate*, stout orange needles (from aqueous methanol), m. p. 149—150° (Found: N, 9·8. $C_{24}H_{20}O_3N_3P$ requires N, 9·8%).

Reaction of Diphenyl Phosphoryl Chloride with Alcohols.—Redistilled *cyclo*hexanol (1·2 mols. 0·52 c.c.) was added to a solution of diphenyl phosphoryl chloride (1 g.) in dry pyridine (4 c.c.), and the mixture kept at room temperature for 20 hours. After dilution with chloroform or carbon tetrachloride (40 c.c), the mixture was washed twice with water and then dried ($MgSO_4$). Evaporation of the solvent afforded a syrupy product from which cyclo*hexyl diphenyl phosphate* was obtained, having b. p. 175—180° (bath-

temp.)/0·03 mm., n^{21} 1·5350. It crystallised on storage, and after recrystallisation from ether–light petroleum (b. p. 40—60°) was obtained as colourless plates, m. p. 34—35° (Found: C, 65·1; H, 6·4. $C_{18}H_{21}O_4P$ requires C, 65·1; H, 6·3%).

Reactions of Diphenyl Phosphoryl Chloride with Phenols.—By use of *p*-nitrophenol and the procedure outlined above, *p-nitrophenyl diphenyl phosphate* was obtained as yellow plates [from ether–light petroleum (b. p. 60—80°)], m. p. 39—40°, b. p. 220—230° (bath-temp.)/0·15 mm., n^{20} 1·5803 (Found: C, 57·9; H, 3·7; N, 4·3. $C_{18}H_{14}O_6NP$ requires C, 58·2; H, 3·8; N, 3·8%).

If β-naphthol was used, *β-naphthyl diphenyl phosphate* was obtained as a viscous yellow liquid, b. p. 270—280° (bath-temp.)/0·03 mm., n^{18} 1·6050 (Found: C, 69·9; H, 4·6. $C_{22}H_{17}O_4P$ requires C, 70·2; H, 4·5%).

Diphenyl phosphoryl chloride and phenol yielded triphenyl phosphate, which formed colourless plates (from ether–light petroleum), m. p. 43—44° (Jacobsen, *loc. cit.*, gave m. p. 41—43° for this compound which he prepared by reaction of phosphorus oxychloride and phenol).

Phosphorylation of 4 : 6-*Benzylidene* α-*Methyl*-2-*deoxy*-D-*galactoside.*—(a) *With phosphorus oxychloride at* −40°. A solution of 4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside (1·0 g.) in dry pyridine (5 c.c.) was cooled to −40°. Phosphorus oxychloride (1·1 mols., 0·38 c.c.) in dry pyridine (2 c.c.) was then added during 20 minutes. The reaction mixture was kept at −40° for 2 hours, then at −10° for a further 2 hours. After recooling to −40°, 10% aqueous pyridine (3 c.c.) was added dropwise and then a small quantity of ice and water was added. When the reaction mixture had warmed, its pH was adjusted to 9·5 (thymolphthalein) by addition of aqueous barium hydroxide solution. The mixture was filtered through a carbon pad and then evaporated to dryness under diminished pressure. *Barium* 4 : 6-*benzylidene* α-*methyl*-2-*deoxy*-D-*galactoside*-3 *phosphate* was obtained as a white amorphous powder very soluble in water from which it could be precipitated by addition of acetone; it had $[\alpha]_D^{26}$ +22·8°, (*c*, 1·6 in water) (Found: P, 6·0; Ba, 29·1. $C_{14}H_{17}O_8PBa$ requires P, 6·5; Ba, 28·5%).

(b) *With diphenyl phosphoryl chloride.* A solution of the benzylidene derivative (3·06 g.) and diphenyl phosphoryl chloride (4 g.) in dry pyridine (16 c.c.) was kept at room temperature for 30 hours. After dilution with ether (75 c.c.), the reaction mixture was washed in turn with water, dilute hydrochloric acid, and again water, and then dried ($MgSO_4$). Evaporation of the solvent afforded a straw-coloured thick syrup (5·4 g., 93%; n^{21} 1·5527), which crystallised on storage. Recrystallisation from the minimum volume of ether gave *diphenyl* 4 : 6-*benzylidene* α-*methyl*-2-*deoxy*-D-*galactoside*-3 *phosphate* as large colourless plates, m. p. 77—78°, $[\alpha]_D^{20}$ +114° (*c*, 0·46 in ethanol) (Found: C, 62·4; H, 5·0. $C_{26}H_{27}O_8P$ requires C, 62·6; H, 5·4%).

4 : 6-*Benzylidene* α-*Methyl*-2-*deoxy*-D-*galactoside*-3 *Phosphoric Acid.*—A solution of diphenyl 4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside-3 phosphate (2 g.) in dry methanol (60 c.c.) was treated with hydrogen at a slight overpressure in the presence of platinum oxide (100 mg.). Uptake of hydrogen (8·9 mols.) was complete in 6 hours. Addition of more catalyst after this period failed to cause any further uptake of hydrogen. After filtration and evaporation of the solvent at 35° (bath-temp.), 4 : 6-*benzylidene* α-*methyl* 2-*deoxy*-D-*galactoside*-3 *phosphoric acid* (1·3 g.) was obtained as a colourless hygroscopic glass, $[\alpha]_D^{20}$ +98° (*c*, 1·3 in water) (Found: P, 9·1. $C_{14}H_{19}O_8P$ requires P, 8·9%).

A solution of this phosphoric acid derivative (50 mg.) in methanol (2 c.c.) was treated with acridine (1 mol., 26 mg.), and the bright yellow solution was evaporated to dryness. After 4 weeks the residue crystallised and when recrystallised from water containing a little ethanol gave the *acridine* salt, m. p. 166—167° (decomp.) (Found: P, 5·6; N, 2·4. $C_{14}H_{19}O_8P,C_{13}H_9N$ requires P, 5·9; N, 2·6%).

2-*Deoxy*-D-*galactose*-3 *Phosphoric Acid.*—4 : 6-Benzylidene α-methyl-2-deoxy-D-galactoside-3 phosphoric acid (0·087 g.) was dissolved in water (4·0 c.c.) and treated with 12N-sulphuric acid (0·8 c.c.) at room temperature. Changes in optical rotation {$[\alpha]_D^{18}$ +87·8° (after 1 minute) ⟶ +55·2° (after 115 minutes)} indicated that hydrolysis was proceeding slowly. The temperature was raised to 40—45° and changes in optical rotation re-observed:

Time (hours)	0	2	4	6
$[\alpha]_D$	+55·2°	+40·8°	+35·3°	+34·2°

The solution was neutralised to pH 8 with aqueous barium hydroxide and the insoluble barium salts were filtered off and washed with water. Addition to the filtrate of an aqueous solution of neutral lead acetate gave only a trace of the lead salt of the hydrolysis product.

In a trial experiment to determine better hydrolysis conditions, α-methyl-2-deoxy-D-galactoside (0·2 g.) dissolved in 0·01N-sulphuric acid (12 c.c.) was heated under reflux and the hydrolysis followed polarimetrically. The following observations were noted:

Time (minutes)	0	15	30
$[\alpha]_D$	+152°	+51·6°	+50·4°

The hydrolysis was essentially complete after 15 minutes and consequently 4 : 6-benzylidene α-methyl 2-deoxy-D-galactoside-3 phosphoric acid (0·22 g.) dissolved in 0·01N-sulphuric acid (12 c.c.) was boiled under reflux for 13 minutes and then the solution was neutralized (to pH 7) by addition of aqueous barium hydroxide. The insoluble barium residues were collected and washed with water. Addition of aqueous neutral lead acetate solution to the combined filtrate and washings gave a flocculent precipitate of the lead salt of 2-deoxy-D-galactose-3 phosphoric acid. This was filtered off, washed several times with water, and dried. It was obtained as a colourless, non-hygroscopic glass which was strongly reducing towards Fehling's solution (Found: P, 6·1. $C_6H_{11}O_8PPb$ requires P, 6·9%). This lead salt (98 mg.), finely ground in an agate mortar, was suspended in water (15 c.c.), and hydrogen sulphide passed through the suspension until decomposition was complete. The precipitated lead sulphide was

filtered off and washed with water and the combined filtrate and washings were freed from hydrogen sulphide by aeration. Evaporation of the solution under diminished pressure gave a straw-coloured glass which was dried with methanol, to yield *2-deoxy-D-galactose-3 phosphoric acid* (25 mg.) as an amorphous powder which strongly reduced Fehling's solution and showed $[\alpha]_D^{20}$ +25° (equilibrium; *c*, 0·5 in water) (Found: P, 12·5. $C_6H_{13}O_8P$ requires P, 12·7%).

Phosphorylation of 3 : 4-iso*Propylidene* α-*Methyl-2-deoxy-D-galactoside.*—(a) *With phosphorus oxychloride at* −40°. A solution of 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galactoside (2 g.) in dry pyridine (10 c.c.) was cooled to −40° and treated during 30 minutes with a solution of phosphorus oxychloride (0·8 g.) in dry pyridine (4 c.c.), also cooled to −40°. The mixture was mechanically agitated throughout the addition. The product was subsequently isolated by the procedure described above and *barium* 3 : 4-iso*propylidene* α-*methyl-2-deoxy-D-galactoside-6 phosphate* (3·39 g., 84·6%) was obtained as a white amorphous powder. It was very soluble in water, giving a clear solution from which it could be precipitated by addition of acetone and had $[\alpha]_D^{20}$ +12° (*c*, 1·49 in water) (Found: P, 6·8; Ba, 30·6. $C_{15}H_{17}O_8PBa$ requires P, 7·2; Ba, 31·4%).

(b) *With diphenyl phosphoryl chloride.* 3 : 4-*iso*Propylidene α-methyl-2-deoxy-D-galactoside (0·93 g.) in dry pyridine (4 c.c.) was treated with diphenyl phosphoryl chloride (1·3 mols., 1·34 g.) at 0° for 10 minutes and then at room temperature overnight. The reaction mixture was then diluted with ether (40 c.c.) and washed successively with water (twice), 0·5N-sulphuric acid (thrice), water, and dilute aqueous sodium hydrogen carbonate. After being dried ($MgSO_4$), the solvent was evaporated and *diphenyl* (3 : 4-iso*propylidene* α-*methyl-2-deoxy-D-galactoside-6*) *phosphate* (1·69 g., 83·7%) was obtained as a pale yellow syrup, $[\alpha]_D^{20}$ +23·9° (*c*, 1·71 in ethanol), n^{17} 1·5140 (Found: C, 58·2; H, 6·2. $C_{22}H_{21}O_8P$ requires C, 58·7; H, 6·0%).

3 : 4-iso*Propylidene* α-*Methyl-2-deoxy-D-galactoside-6 Phosphoric Acid.*—A solution of the diphenyl phosphate (2·81 g.) in methanol (90 c.c.) and water (30 c.c.) was freed from catalyst poisons (traces) by being boiled under reflux for 10 minutes with activated charcoal (2 g.). The charcoal was filtered off and washed with a little hot methanol. The combined filtrate and washings were shaken in hydrogen at a slight overpressure with Adams's platinum oxide (150 mg.). Absorption of hydrogen (1220 c.c.) was complete in 3 hours. The solution was filtered from the catalyst and evaporated to dryness under diminished pressure. 3 : 4-iso*Propylidene* α-*methyl-2-deoxy-D-galactoside-6 phosphoric acid* (1·6 g.) was obtained as a colourless hygroscopic glass, $[\alpha]_D^{20}$ +53·7° (*c*, 1·2 in water) (Found: P, 11·0. $C_{16}H_{19}O_8P$ requires P, 10·5%). This compound rapidly coloured on storage. It did not yield a crystalline acridine salt.

2-Deoxy-D-galactose-6 Phosphoric Acid.—3 : 4-*iso*Propylidene α-methyl-2-deoxy-D-galactoside-6 phosphoric acid (1·8 g.) in solution in water (100 c.c.) was treated with 0·6N-sulphuric acid (1·7 c.c.). The solution was boiled gently under reflux and the ensuing hydrolysis was followed polarimetrically and was complete in 38 minutes. The solution was neutralised to pH 8 by the addition of aqueous barium hydroxide, the insoluble barium residues were collected and washed with water, and the washings added to the filtrate which was then treated with excess of neutral lead acetate solution. The flocculent precipitate was collected by centrifuging and washed five times by centrifuging with water. It was suspended in water and decomposed with hydrogen sulphide. The product was worked up in the usual manner and the colourless solution so obtained evaporated to dryness under diminished pressure. A colourless syrup (0·54 g.) was obtained which solidified on trituration with methanol. *2-Deoxy-D-galactose-6 phosphoric acid* was obtained as a non-hygroscopic white powder which strongly reduced Fehling's solution and showed m. p. 155—160° (decomp.), $[\alpha]_D^{20}$ +41° (equilibrium; *c*, 0·41 in water) (Found: P, 12·9. $C_6H_{13}O_8P$ requires P, 12·7%).

4 : 6-*Ethylidene* 1 : 2-iso*Propylidene* D-*Galactose.*—D-Galactose (30 g.) was mechanically agitated with freshly distilled paraldehyde (110 c.c.) and concentrated sulphuric acid (0·3 c.c.), at room temperature for 24 hours. The resulting semi-solid mass was filtered off, dissolved in dioxan, and, after cooling, filtered from unchanged D-galactose. Evaporation of the filtrate afforded syrupy 4 : 6-ethylidene D-galactose (21 g.) which was strongly reducing towards Fehling's reagent. It was dissolved in acetone (350 c.c.) containing anhydrous zinc chloride (35 g.) and shaken at room temperature for 24 hours. The reaction mixture was poured into water containing an excess of sodium carbonate, and the precipitated zinc residues were collected and washed with acetone. Evaporation of the acetone from the combined filtrate and washings left an aqueous solution which was extracted with chloroform (3 × 100 c.c.). After drying ($MgSO_4$), the extract was evaporated and the residue distilled. 4 : 6-Ethylidene 1 : 2-*iso*propylidene D-galactose was obtained as a colourless hygroscopic liquid, b. p. 125—130°/(bath-temp.)/0·05 mm., n^{17} 1·4710, $[\alpha]_D^{20}$ −55·7° (*c*, 2·06 in chloroform). Because of the hygroscopic nature of this compound it was not possible to obtain good results for elemental analysis, but its identity was fully substantiated by the following derivatives.

4 : 6-*Ethylidene* 1 : 2-iso*Propylidene* 3-*Toluene*-p-*sulphonyl* D-*Galactose.*—A solution of the ethylidene *iso*propylidene derivative (0·61 g.) in dry pyridine (2·5 c.c.) was treated with toluene-*p*-sulphonyl chloride (0·6 g., 1·2 mols.) at room temperature for 12 hours. The reaction mixture was poured into water, and an oil separated which soon solidified. Recrystallisation of it from aqueous ethanol gave 4 : 6-*ethylidene* 1 : 2-iso*propylidene* 3-*toluene*-p-*sulphonyl* D-*galactose* as colourless needles, m. p. 106—107°, $[\alpha]_D^{20}$ −67·3° (*c*, 1·3 in chloroform) (Found: C, 53·7; H, 5·9. $C_{19}H_{24}O_8S$ requires C, 54·0; H, 6·0%).

4 : 6-*Ethylidene* 3-*Methanesulphonyl* 1 : 2-iso*Propylidene* D-*Galactose.*—In a similar manner to that described, 4 : 6-*ethylidene* 3-*methanesulphonyl* 1 : 2-iso*propylidene* D-*galactose* was prepared from ethylidene *iso*propylidene D-galactose (0·33 g.) in dry pyridine (15 c.c.) and methanesulphonyl chloride (0·27 g., 1·2 mols.). When recrystallised from aqueous ethanol it was obtained as colourless needles, m. p. 98—99°, $[\alpha]_D^{20}$ −52·9° (*c*, 0·7 in chloroform) (Found: C, 44·3; H, 6·4. $C_{13}H_{22}O_8S$ requires C, 44·4; H, 6·2%).

The toluene-*p*-sulphonyl and methanesulphonyl derivatives (200 mg.) were separately dissolved in acetone (5 c.c.) containing excess of sodium iodide (500 mg.) and heated at 130—135° for 10 hours. There was no reaction in either case.

Phosphorylation of 4 : 6-*Ethylidene* 1 : 2-iso*Propylidene* D-*Galactose*.—(a) *With phosphorus oxychloride at* −40°. To a solution of 4 : 6-ethylidene 1 : 2-*iso*propylidene D-galactose (2·0 g.) in dry pyridine (10 c.c.) cooled to −40°, a solution of phosphorus oxychloride (0·8 c.c.) in dry pyridine (5 c.c.), also cooled to −40°, was added during 20 minutes with vigorous mechanical stirring. The product was isolated in the usual manner and *barium* 4 : 6-*ethylidene* 1 : 2-*isopropylidene* D-*galactose*-3 *phosphate* (3·5 g., 77%) was obtained as an amorphous white powder, soluble in water from which it could be precipitated by addition of acetone. Fractionation by this method gave a product showing $[\alpha]_D^{20}$ −24° (*c*, 1·4 in water) (Found : P, 6·8; Ba, 28·2. $C_{11}H_{17}O_9PBa$ requires P, 6·7; Ba, 29·7%).

(b) *With diphenyl phosphoryl chloride*. A solution of the ethylidene *iso*propylidene galactose (2·74 g.) in dry pyridine (11 c.c.) was cooled at 0° and treated with a solution of diphenyl phosphoryl chloride (3·5 g., 1·3 mols.) in dry pyridine (6 c.c.) for 10 minutes and then at room temperature for 24 hours. The mixture was diluted with ether (100 c.c.) and washed successively with water, 0·5N-sulphuric acid, water, and dilute aqueous sodium hydrogen carbonate. After drying ($MgSO_4$) it was evaporated and afforded (4 : 6-*ethylidene* 1 : 2-iso*propylidene* D-*galactose*-3) *diphenyl phosphate* (4·9 g., 76·5%), $[\alpha]_D^{20}$ −42·6° (*c*, 1·4 in ethanol), n^{17} 1·5200 (Found : C, 57·6; H, 5·5. $C_{22}H_{27}O_9P$ requires C, 57·7; H, 5·6%).

4 : 6-*Ethylidene* 1 : 2-iso*Propylidene* D-*Galactose*-3 *Phosphoric Acid*.—A solution of the above diphenyl phosphate (1·66 g.) in ethanol (60 c.c.) and water (20 c.c.) was freed from catalyst poisons, either by being shaken for 2 hours in an atmosphere of hydrogen at a slight overpressure in the presence of palladium black (2 g.) or, better, boiled under reflux with activated charcoal (2 g.) for 10 minutes. It was then shaken vigorously in an atmosphere of hydrogen at a slight overpressure in the presence of platinum oxide (100 mg.). Uptake of hydrogen (8 mols., 610 c.c.) was complete after 4·5 hours and the solution was filtered from catalyst and evaporated to dryness under diminished pressure. 4 : 6-Ethylidene 1 : 2-*iso*propylidene D-galactose-3 phosphoric acid (0·8 g.) was obtained as a water-soluble, hygroscopic glass, $[\alpha]_D^{18}$ −41·5° (*c*, 0·77 in water) (Found : P, 9·4. $C_{11}H_{19}O_9P$ requires P, 9·2%). This phosphoric acid derivative (100 mg.) was dissolved in methanol (1 c.c.) and treated with a solution of acridine (55 mg.) in methanol (1 c.c.). On addition of ether the *acridine* salt separated as very small bright yellow rods, m. p. 162—163° (with darkening), 171—172° (decomp.) (Found : P, 6·0; N, 2·7. $C_{11}H_{19}O_9P,C_{13}H_9N$ requires P, 6·1; N, 2·7%).

D-*Galactose*-3 *Phosphoric Acid*.—A solution of 4 : 6-ethylidene 1 : 2-*iso*propylidene D-galactose-3 phosphoric acid (1·57 g.) in water (100 c.c.) containing N-sulphuric acid (1 c.c.) was boiled under reflux for 1 hour. After neutralisation to pH 7·5 by addition of aqueous barium hydroxide and removal of the precipitated barium sulphate, the solution was treated with excess of aqueous neutral lead acetate solution. The flocculent precipitate was collected and washed by centrifuging with water. It was then suspended in warm water and decomposed by hydrogen sulphide. After removal of the lead sulphide, the filtrate was aerated to remove dissolved hydrogen sulphide and then evaporated to small bulk under diminished pressure. Dilute aqueous potassium hydroxide was added (to pH 7·2) and the solution re-evaporated. A colourless syrup (0·42 g., 42%) was obtained which crystallised in triangular plates on storage over phosphoric oxide. *Dipotassium* D-*galactose*-3 *phosphate dihydrate* was obtained as colourless small plates, $[\alpha]_D^{18}$ +25·2° (*c*, 0·81 in water) (Found : C, 18·7; H, 4·2; P, 8·4. $C_6H_{11}O_9PK_2,2H_2O$ requires C, 19·3; H, 4·1; P, 8·3%). It was very soluble in water and readily reduced Fehling's reagent.

The dipotassium salt (75 mg.) was converted into the lead salt by addition of excess of aqueous neutral lead acetate solution, and the lead salt in turn converted into the free phosphoric acid by hydrogen sulphide. The aqueous solution of the free phosphoric acid was shaken with solid acridine (200 mg.) for 5 hours. Undissolved solid material was filtered off and the filtrate evaporated to a syrup which crystallised on trituration with methanol. The *acridine* salt of D-galactose-3 phosphoric acid was obtained as fine yellow needles, m. p. 180—185° (Found : N, 2·7. $C_6H_{13}O_9P,C_{13}H_9N$ requires N, 3·1%).

Phosphorylation of 1 : 2-3 : 4-*Diisopropylidene* D-*Galactose*.—(a) *With phosphorus oxychloride at* −40°. A solution of the di*iso*propylidene derivative (2 g.) (Grunenberg *et al.*, *J. Amer. Chem. Soc.*, 1938, **60**, 1507) in dry pyridine (10 c.c.) was cooled to −40° and treated with a solution of phosphorus oxychloride (1·1 mols., 0·7 c.c.) in dry pyridine (5 c.c.), also cooled to −40°. The addition was made during 20 minutes to a vigorously stirred solution. The reaction mixture was then treated as already described, and barium 1 : 2-3 : 4-*iso*propylidene D-galactose-6 phosphate was obtained as an amorphous white powder, $[\alpha]_D^{20}$ −17·9° (*c*, 1·6 in water).

(b) *With diphenyl phosphoryl chloride*. 1 : 2-3 : 4-Di*iso*propylidene D-galactose (2 g.) was dissolved in dry pyridine (8 c.c.) cooled to 0°, and treated with diphenyl phosphoryl chloride (2·43 g.) also in solution in dry pyridine (4 c.c.) at 0°. After 10 minutes at 0° the mixture was kept overnight at room temperature, diluted with ether (50 c.c.), and worked up as previously described. (1 : 2-3 : 4-*Diisopropylidene* D-*galactose*-6) *diphenyl phosphate* (2·74 g., 76·5%) was obtained as a straw-coloured syrup, n^{17} 1·5150, $[\alpha]_D^{20}$ −30·9° (*c*, 1·4 in ethanol) (Found : C, 58·5; H, 5·9. $C_{24}H_{29}O_9P$ requires C, 58·4; H, 5·9%).

1 : 2-3 : 4-*Diisopropylidene* D-*Galactose*-6 *Phosphoric Acid*.—A solution of the above diphenyl 6-phosphate (2·2 g.) in ethanol (60 c.c.) and water (15 c.c.) was boiled under reflux with activated charcoal (2·5 g.) for 10 minutes. After filtration, the solution was shaken with platinum oxide (100 mg.) in an atmosphere of hydrogen at a slight overpressure. Hydrogen (830 c.c., 8·3 mols.) was absorbed during 6 hours. Filtration and evaporation of the solution afforded 1 : 2-3 : 4-di*iso*propylidene D-galactose-6 phosphoric acid (1·2 g.) as a colourless glass, $[\alpha]_D^{20}$ −20·1° (*c*, 1·6 in water). Treatment of this derivative (100 mg.) in methanol (3 c.c.) with acridine (55 mg.), followed by slow evaporation of the

solution, yielded the *acridine* salt as large yellow plates, m. p. 162—164° (Found: P, 6·4; N, 2·7. $C_{13}H_{21}O_9P,C_{13}H_9N$ requires P, 5·9; N, 2·7%).

D-*Galactose*-6 *Phosphoric Acid.*—1 : 2-3 : 4-Di*iso*propylidene D-galactose-6 phosphoric acid (1·2 g.) in solution in water (100 c.c.) containing 5N-sulphuric acid (6 c.c.) was boiled under reflux for 1 hour. Addition of aqueous barium hydroxide (to pH 8) and removal of the insoluble barium residues by filtration afforded a solution to which excess of aqueous neutral lead acetate solution was added. The lead salt was obtained as a gelatinous precipitate which was washed at the centrifuge several times with water. It was decomposed by hydrogen sulphide in the usual manner and D-galactose-6 phosphoric acid was obtained as a colourless glass (0·51 g., 50·9%), $[\alpha]_D^{20}$ +36·5° (*c*, 0·6 in water) (Found: P, 12·0. Calc. for $C_6H_{13}O_9P$: P, 11·9%). Levene and Raymond (*loc. cit.*) gave $[\alpha]_D^{25}$ +24·5° in water for the barium salt.

Our thanks are offered to the British Empire Cancer Campaign (Birmingham Branch) for financial assistance. One of us (A. B. F.) thanks the Brewing Industry Research Foundation for a personal grant.

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220. *Deoxy-sugars. Part XVI. A Study of the Stabilities of Some Phosphoric Acid Derivatives of* D-*Galactose and* 2-*Deoxy*-D-*galactose.*

By A. B. FOSTER, W. G. OVEREND, and M. STACEY.

The rates of dephosphorylation of certain phosphoric acid derivatives of D-galactose and 2-deoxy-D-galactose by acid and alkaline reagents and also by an enzyme isolated from *Actinomyces* strain A, have been investigated. Results obtained confirm the view that in 2-deoxyhexoses the methylene (deoxy) group renders substituents in the molecule relatively more labile than in the normal hexose analogue.

IN the preceding paper the syntheses were described of galactose-3 and -6 phosphoric acid and of the corresponding 2-deoxy-analogues. In common with most phosphoric acid derivatives of sugars, these compounds were difficult to crystallize and characterize, but they have been purified as their acridine salts. In further work with these compounds it was decided to measure their comparative rates of dephosphorylation.

The action of dilute aqueous mineral acids on the phosphoric acid derivatives of sugars has been employed by numerous workers as a means of correlating the lability of the phosphoric acid residue with its position in the sugar molecule. For example, recent results which Todd and Michelson (*J.*, 1949, 2476) obtained by this method clearly indicate that, in the ribose molecule, a phosphoric acid residue located at position 3 of the sugar is the most labile. Phosphoric esters at positions 2 and 5 in this sugar molecule are definitely less labile. Gulland and Smith (*J.*, 1947, 338) have employed similar methods with uridine-2′ phosphate, and Friedkin (*J. Biol. Chem.*, 1950, **184**, 449) has shown that 50% of the phosphorus of deoxyribose-1 phosphate is released as inorganic phosphate within 10—15 minutes on hydrolysis at pH 4 at 23°.

We have used this method, employing 0·1N-sulphuric acid, to study the lability of the phosphoric acid derivatives of D-galactose and 2-deoxy-D-galactose already described.

Briefly, the technique adopted was to heat aliquots (2 c.c.) of a solution (1 mg. of P/c.c.) of the phosphoric acid derivative in 0·1N-sulphuric acid, in sealed glass tubes, on a boiling water-bath. At suitable intervals the liberated phosphate ion was estimated colorimetrically (Allen, *Biochem. J.*, 1940, **34**, 858). It was found that D-galactose-3 phosphoric acid was more labile than the corresponding 6-phosphoric acid, in agreement with the work described above (Todd and Michelson, *loc. cit.*). For the derivatives of 2-deoxy-D-galactose, it was shown that the phosphoric acid residues located at both $C_{(3)}$ and $C_{(6)}$ in the sugar are much more labile under acid conditions than are the residues in the corresponding derivatives of D-galactose. The hydrolyses are represented graphically in Fig. 1. It is seen that 2-deoxy-D-galactose-3 phosphoric acid had undergone 84% hydrolysis in 5 hours whereas in the same time the corresponding derivative of D-galactose had undergone only 13% hydrolysis. The activation of the phosphoric acid residue in this derivative of 2-deoxy-D-galactose may be attributed to the presence of the methylene (deoxy) group at position 2. The influence of this group on the glycosidic centre in 2-deoxy-hexoses and -pentoses has already been reported

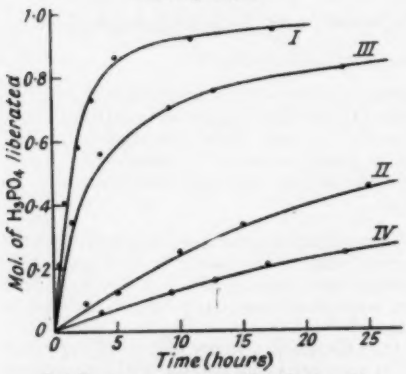
(Stacey *et al.*, *J.*, 1949, 2836, 2846; 1950, 671, 738). It was shown particularly that the glycosidic methyl group in sugars of this type was much more labile than that in the corresponding hexose series. The present work has confirmed this finding (see Fig. 2).

More surprising than the above results was the fact that the lability of the phosphoric acid residue at position 6 in 2-deoxy-D-galactose was greater than that in the corresponding derivative of D-galactose. From Fig. 1 it can be seen that in 5 hours 2-deoxy-D-galactose-6 phosphoric acid had undergone 58% hydrolysis, whereas the corresponding derivative of D-galactose had only undergone 7% hydrolysis. These facts appear to indicate that the methylene (deoxy) group at position 2 in the deoxy-sugar does not merely activate the substituents at the adjacent $C_{(1)}$ and $C_{(3)}$, but activates the molecule as a whole, although the degree of activation of substituents at the adjacent positions 1 and 3 is greater than that of substituents at the more remote position 6.

When the phosphoric acid derivatives of 2-deoxy-D-galactose and of D-galactose were submitted to treatment with 0·1N-sodium hydroxide under conditions analogous to those employed in the acid treatment described above, dephosphorylation was essentially complete in each case in 5 minutes. The rapid rate of dephosphorylation is probably not caused solely

FIG. 1.

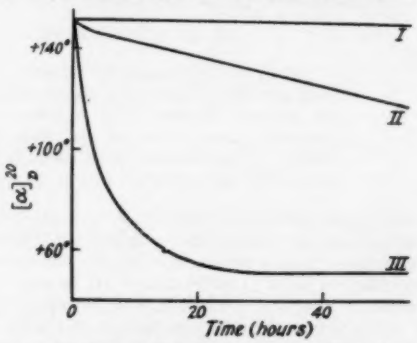
Acid hydrolysis.



I, 2-*Deoxy*-D-*galactose*-3 *phosphoric acid.*
II, D-*Galactose*-3 *phosphoric acid.*
III, 2-*Deoxy*-D-*galactose*-6 *phosphoric acid.*
IV, D-*Galactose*-6 *phosphoric acid.*

FIG. 2.

*Hydrolysis of α-methyl-*D*-galactoside and α-methyl-2-deoxy-*D*-galactoside with sulphuric acid.*



I, α-*Methyl*-D-*galactoside in* 2N-*sulphuric acid.*
II, α-*Methyl*-D-*galactoside in* 12N-*sulphuric acid.*
III, α-*Methyl-2-deoxy*-D-*galactoside in* 2N-*sulphuric acid.*

by the lability of the phosphoric acid substitutents towards alkali, since, as is well known, sugar derivatives having a free reducing group are rapidly transformed and destroyed by being heated with alkali, and phosphoric acid would be liberated.

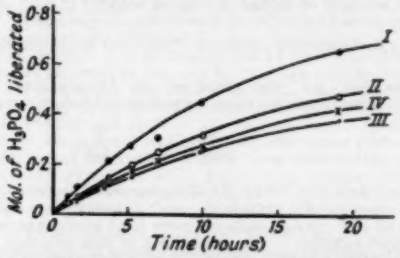
The mechanism of changes undergone during alkaline dephosphorylation needs careful investigation. It should be noted that Percival and Percival (*J.*, 1945, 874) found a slower hydrolysis for methylglucoside phosphates, *i.e.*, where the $C_{(1)}$ is blocked and other hydroxyl groups are free, and we now have shown that alkaline hydrolysis of certain phosphoric esters of D-galactose and 2-deoxy-D-galactose in which $C_{(1)}$ is blocked resulted in a comparatively large decrease in the rate of dephosphorylation. The rates of alkaline dephosphorylation of 4 : 6-benzylidene α-methyl-2-deoxy-D-galactoside-3 phosphoric acid, 3 : 4-*iso*propylidene α-methyl-2-deoxy-D-galactoside-6 phosphoric acid, 4 : 6-ethylidene 1 : 2-*iso*propylidene D-galactose-3 phosphoric acid, and 1 : 2-3 : 4-di*iso*propylidene D-galactose-6 phosphoric acid, are represented graphically in Fig. 3. It is clear from the graphs that on increasing the strength of the alkali to 1·0N, hydrolysis of the most labile phosphoric acid derivative, namely, 4 : 6-benzylidene α-methyl-2-deoxy-D-glactoside-3 phosphoric acid, was 65% complete after 20 hours.

Finally the rates of enzymic dephosphorylation were compared. The enzyme used was isolated from the bacteriolytic system of *Actinomyces* strain A described by Muggleton and Webb (*Biochim. Biophys. Acta*, in the press). It was obtained from a purified culture filtrate from organisms growing on a synthetic medium and was isolated by dialysis and dried from the

frozen state. The enzyme mixture was complex but contained a phosphatase which could effect the dephosphorylation of the sugar phosphates under examination. Fig. 4 shows the liberation of phosphoric acid with time, at pH 7 and 37°, by the action of the enzyme on dilute aqueous solutions of 2-deoxy-D-galactose-3 and -6 phosphoric acid and of the corresponding derivatives of D-galactose. It can be seen that the derivatives of D-galactose were dephosphorylated slowly (20% in 23 hours) and approximately at the same rate. The corresponding derivatives of 2-deoxy-D-galactose were dephosphorylated much more rapidly, for in 23 hours 2-deoxy-D-galactose-3 phosphoric acid had undergone 66% dephosphorylation and the 6-phosphoric acid had been dephosphorylated to the extent of 32%. The rapid decrease

FIG. 3.

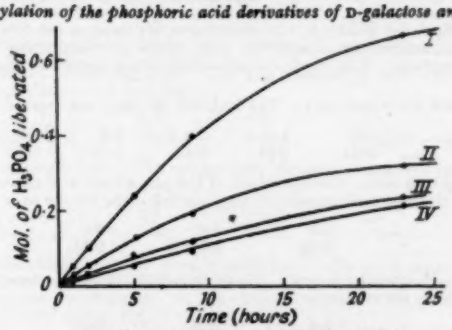
Alkaline hydrolysis of the phosphoric acid derivatives of D-*galactose and 2-deoxy-*D-*galactose.*



I, ● 4 : 6-*Benzylidene α-methyl-2-deoxy-*D-*galactoside-3 phosphoric acid.*
II, ○ 3 : 4-iso*Propylidene α-methyl-2-deoxy-*D-*galactoside-6 phosphoric acid.*
III, — · — 1 : 2-3 : 4-*Diisopropylidene* D-*galactose-6 phosphoric acid.*
IV, × 4 : 6-*Ethylidene* 1 : 2-iso*propylidene* D-*galactose-3 phosphoric acid.*

FIG. 4.

Enzymic dephosphorylation of the phosphoric acid derivatives of D-*galactose and 2-deoxy-*D-*galactose.*



I, 2-*Deoxy-*D-*galactose-3 phosphoric acid.*
II, 2-*Deoxy-*D-*galactose-6 phosphoric acid.*
III, D-*Galactose-6 phosphoric acid.*
IV, D-*Galactose-3 phosphoric acid.*

in the rates of dephosphorylation after 10 hours may be due to several causes. For example, as the enzymic hydrolysis proceeded, the liberated phosphoric acid displaced the pH of the solution towards the acid region. This effect was not completely counteracted by the veronal buffer used and tended to inhibit the action of the enzyme. This buffer was employed instead of the more usual phosphate buffer, because the enzymic hydrolysis was followed by phosphorus determinations (see Experimental section).

The results described may be interpreted as indicating that the phosphoric acid residue located at position 3 in the 2-deoxy-D-galactose molecule is considerably activated in comparison with that in the corresponding hexose derivative. This may be attributed to the influence of the methylene group at position 2 in the former substance. In agreement with the suggestion made earlier that the molecule of 2-deoxy-D-galactose as a whole is activated by the methylene

group is the fact that the 6-phosphoric acid derivative of the deoxy-sugar is also more rapidly dephosphorylated by the enzyme than is the corresponding D-galactose-6 phosphoric acid.

Experimental.

Hydrolysis of α-Methyl-2-deoxy-D-galactoside with Sulphuric Acid.—α-Methyl-2-deoxy-D-galactoside (0·1 g.) was dissolved in water (5 c.c.) ($[\alpha]_D^{20}$ +152° for this solution), and 12N-sulphuric acid (1·0 c.c.) was added. The ensuing hydrolysis was followed polarimetrically :

Time (hours)	0·03	0·3	1·03	2·25	5·75	17·75	29	40
$[\alpha]_D^{20}$	+150°	+145°	+133°	+114°	+84°	+62°	+52°	+52°

Neutralisation of the solution with barium carbonate followed by removal of the insoluble barium residues and evaporation of the solvent afforded a syrupy product, which readily reduced Fehling's solution. Treatment with a solution of aniline (0·1 g.) in ethanol (2 c.c.) yielded 2-deoxy-D-galactose anilide, m. p. 131—132° alone or on admixture with an authentic specimen.

Hydrolysis of α-Methyl-D-galactoside with Sulphuric Acid.—(*a*) 2N-Sulphuric acid had no effect on the glycoside after 5 days.

(*b*) α-Methyl-D-galactoside (0·1 g.) was dissolved in 12N-sulphuric acid (5 c.c.) and the following changes in optical rotation of the solution were observed polarimetrically :

Time (hours)	0	2	10	50
$[\alpha]_D^{20}$	+150°	+148°	+143°	+120°

Hydrolysis of the Phosphoric Acid Derivatives of D-Galactose and 2-Deoxy-D-galactose.—(a) *By sulphuric acid.* The lead salt of the appropriate phosphoric acid derivative (*ca.* 40 mg.), after being finely powdered and dried *in vacuo* at 100° over phosphoric oxide for 5 hours, was suspended in water (10 c.c.) and decomposed with hydrogen sulphide. The precipitate of lead sulphide was collected and washed by grinding it under water. After a second treatment with hydrogen sulphide the combined filtrate and washings were freed from hydrogen sulphide by aeration. The volume was made up to 25 c.c. and 0·6N-sulphuric acid (6 c.c.) was added. Aliquots (2 c.c.) of the resultant solution were sealed in Pyrex glass tubes and immersed in a bath at 100°. At suitable intervals, the tubes were opened and the contents washed carefully into a standard flask (25 c.c.). After dilution with water, perchloric acid (2 c.c.; 60% solution; *d* 1·54), amidol reagent [2 c.c. of a solution containing amidol (2 g.) and sodium hydrogen sulphite (40 g.) in water (200 c.c.)], 8·3% aqueous ammonium molybdate (1 c.c.), and water (to 25 c.c.) were added successively. The blue colour which developed was measured after 15—30 minutes in a Hilger (Spekker) photoelectric absorptiometer using a red filter (Ilford H.608). The values obtained were standardized by comparison with values obtained using a standard solution of potassium dihydrogen phosphate. This method of determination is essentially that of Allen (*Biochem. J.*, 1940, **34**, 858).

(i) *2-Deoxy-D-galactose-3 phosphoric acid.* The lead salt (37 mg.) was treated as above :

Time (hours)	0·5	1·1	2·1	3·0	5·0	11·0	17·5
H_3PO_4, mols. liberated	0·21	0·41	0·58	0·73	0·86	0·92	0·95

(ii) *D-Galactose-3 phosphoric acid.* On hydrolysis of the phosphoric acid derivative obtained from its lead salt (36 mg.) or from the dipotassium salt (27 mg.) the following results were obtained :

Time (hours)	2·5	5·0	10·0	15·0	25·0
H_3PO_4, mols. liberated	0·09	0·13	0·25	0·33	0·45

(iii) *2-Deoxy-D-galactose-6 phosphoric acid.* This compound (20 mg.) was hydrolysed according to the procedure described, with the results :

Time (hours)	1·5	3·75	9·25	12·75	23·0
H_3PO_4, mols. liberated	0·35	0·56	0·70	0·75	0·82

(iv) *D-Galactose-6 phosphoric acid.* Hydrolysis of this compound (20 mg.) gave the results :

Time (hours)	3·75	9·25	12·75	17·0	23·0
H_3PO_4, mols. liberated	0·06	0·12	0·16	0·20	0·24

(b) *By sodium hydroxide.* A solution of the free phosphoric acid derivative was made from the lead salt according to the procedure described. The solution was diluted with 0·6N-aqueous sodium hydroxide (5 c.c.), and aliquots (2 c.c.) were sealed in tubes and the liberated phosphate ion determined as previously described. 2-Deoxy-D-galactose-3 phosphoric acid and D-galactose-3 phosphoric acid were 90% hydrolysed in less than 30 minutes and the corresponding 6-phosphoric acid derivatives were 90% hydrolysed in less than 10 minutes.

(i) 4 : 6-Benzylidene α-methyl-2-deoxy-D-galactoside-3 phosphoric acid (29 mg.) was dissolved in water (25 c.c.) and 6N-sodium hydroxide (5 c.c.) was added. Aliquots (2 c.c.) of this solution were treated as described previously, and the released phosphate ion was determined :

Time (hours)	1·0	1·75	3·75	5·25	7·0	10·0	19·0
H_3PO_4, mols. liberated	0·075	0·11	0·22	0·27	0·30	0·43	0·65

(ii) 4 : 6-Ethylidene 1 : 2-*iso*propylidene D-galactose-3 phosphoric acid (25 mg.) was hydrolysed in a similar manner :

Time (hours)	1·0	1·75	3·75	5·25	7·0	10·0	19·0
H_3PO_4, mols. liberated	0·05	0·07	0·12	0·17	0·22	0·27	0·42

(iii) 3 : 4-*iso*Propylidene α-methyl-2-deoxy-D-galactoside-6 phosphoric acid (23 mg.) was treated according to the same procedure :

Time (hours)	1·0	1·75	3·75	5·25	7·0	10·0	19·0
H_3PO_4, mols. liberated	0·04	0·07	0·15	0·20	0·25	0·27	0·48

(iv) 1 : 2-3 : 4-Di*iso*propylidene-D-galactose-6 phosphoric acid (25 mg.) was hydrolysed as described above :

Time (hours)	1·0	3·75	5·25	7·0	10·0	19·0
H_3PO_4, mols. liberated	0·054	0·11	0·15	0·18	0·25	0·38

Enzymic Dephosphorylation of the Phosphoric Acid Derivatives of D-*Galactose and* 2-*Deoxy*-D-*galactose.*—Samples of the phosphoric acid derivative (*ca.* 20 mg.) were dissolved in water (*ca.* 15 c.c.), and the pH of the solution was adjusted to 6·9—7·1 by titration with 0·1N-sodium hydroxide (end-point determined by pH meter). The solution was diluted to 25 c.c. and treated with veronal buffer (9·4 c.c. of a solution containing 2·02 g. of sodium diethylbarbiturate per 100 c.c.) and 0·1N-hydrochloric acid (8·6 c.c.). The solution (*A*) was warmed at 37°. The enzyme from *Actinomyces* strain A (0·5 g., kindly supplied by Dr. Webb and Dr. Muggleton) was extracted with water (110 c.c.) at room temperature for 30 minutes. Insoluble debris and denatured protein were removed by centrifuging and the straw-coloured supernatant liquid was warmed to 37°. The enzyme solution (25 c.c.) was added to solution *A* and after being shaken the mixture was incubated at 37°. At suitable intervals, samples (5 c.c.) were withdrawn and the inorganic phosphorus was determined by Allen's method (*loc. cit.*).

(a) 2-*Deoxy*-D-*galactose*-3 *phosphoric acid.* The lead salt (37 mg.), converted into the free phosphoric acid by means of hydrogen sulphide as already described, was dissolved in water (25 c.c.) and treated as above :

Time (hours)	0·8	1·9	5·1	9·1	23
H_3PO_4, mols. liberated	0·059	0·097	0·244	0·40	0·66

(b) D-*Galactose*-3 *phosphoric acid.* The dipotasium salt (26 mg.), dissolved in water (25 c.c.), released phosphorus under the influence of the enzyme as shown :

Time (hours)	5·0	9·1	23
H_3PO_4, mols. liberated	0·046	0·094	0·21

(c) 2-*Deoxy*-D-*galactose*-6 *phosphoric acid.* The free phosphoric acid (20 mg.), dissolved in water (25 c.c.), was dephosphorylated as shown below :

Time (hours)	0·9	1·9	5·1	9·1	23
H_3PO_4, mols. liberated	0·038	0·064	0·132	0·185	0·32

(d) D-*Galactose*-6 *phosphoric acid.* The syrupy free phosphoric acid (20 mg.) was dephosphorylated as follows :

Time (hours)	0·9	1·9	5·2	9·2	23
H_3PO_4, mols. liberated	0·022	0·032	0·088	0·103	0·23

The veronal buffer described above was used in preference to the more usual phosphate buffer, because the concentration of phosphate ion would have been too great to permit accurate measurements of the small amounts of phosphate ion liberated. All the hydrolyses described in this paper were carried out in duplicate. Errors did not exceed 3%.

The authors thank the British Empire Cancer Campaign (Birmingham Branch) for financial assistance. One of them (A. B. F.) is indebted to the Brewing Industry Research Foundation for a personal grant.

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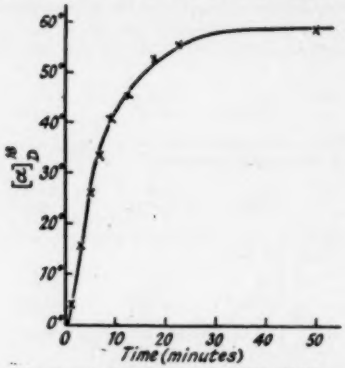
[*Received, November 29th,* 1950.]

221. *Deoxy-sugars. Part XVII. An Investigation of the Glycal Method for the Preparation of Derivatives of 2-Deoxy-D-galactose.*

By W. G. Overend, F. Shafizadeh, and M. Stacey.

The glycal method for the preparation of derivatives of 2-deoxy-D-galactose has been investigated. No evidence has been obtained for the formation of a stable intermediate ester when D-galactal is converted into 2-deoxy-D-galactose by treatment with dilute sulphuric acid. It is shown that the addition of methanol to galactal and triacetyl galactal follows the same course (cf. Fischer, Bergmann, and Schotte, *Ber.*, 1920, **53**, 517).

Recently the preparation and properties of some derivatives of 2-deoxy-D-galactose were described (Overend, Shafizadeh, and Stacey, *J.*, 1950, 671). For these experiments 2-deoxy-β-D-galactose was prepared from D-galactose by the well-known glycal method. Levene and Tipson (*J. Biol. Chem.*, 1931, **93**, 644) first used this procedure for the preparation of 2-deoxy-D-galactose and more recently it was likewise employed by Pigman and Isbell (*J. Res. Nat. Bur. Stand.*, 1939, **22**, 397). The latter workers assumed that on treatment of D-galactal with dilute sulphuric acid the deoxy-sugar was formed *via* an intermediate ester which was hydrolysed when heated with barium carbonate at 60° for a relatively long period. We originally adopted



Treatment of D-*galactal with* 5% H_2SO_4.

this method but now have found that 2-deoxy-D-galactose can be obtained in considerably improved yield by introducing a rapid neutralisation of the reaction mixture with barium hydroxide at room temperature. Moreover, potentiometric titrations with N-potassium carbonate of 5% aqueous sulphuric acid containing D-galactal or D-glucal did not materially differ from those of 5% aqueous sulphuric acid alone, thereby indicating that the acid concentration was not decreased by entering into stable ester formation with the glycal. Polarimetric observation of a solution of D-galactal in dilute sulphuric acid indicated that the reaction yielded directly 2-deoxy-D-galactose since the final value for the optical rotation of the solution was the same as that of the deoxy-sugar in similar sulphuric acid solution (see figure). Whether an unstable transient ester is formed is not known, but it would appear that the process described by Pigman and Isbell (*loc. cit.*) as hydrolysis by barium carbonate was merely slow heterogeneous-phase neutralisation of sulphuric acid by barium carbonate.

Fischer, Bergmann, and Schotte (*Ber.*, 1920, **53**, 517) recorded that triacetyl D-glucal and hydrogen bromide in acetic acid gave a crystalline " diacetyl D-glucal hydrobromide " which on re-acetylation yielded " triacetyl D-glucal hydrobromide." The bromine atoms in these compounds were stated to be inert towards silver nitrate, a behaviour which supported Fischer's view that these were 2-bromo-2-deoxy-sugar derivatives. This opinion seemed to be difficult to accept since, in the above-described " glycal procedure " the addition of water to glycals in the presence of dilute sulphuric acid to give 2-deoxy-sugars, the opposite type of orientation is obtained, the anion becoming attached to $C_{(1)}$. Repetition of this work by Davoll and Lythgoe

(*J.*, 1949, 2526) yielded a syrup which behaved as 3 : 4 : 6-triacetyl 1-bromo-1 : 2-dideoxyglucose since on condensation with silver theophylline followed by deacetylation they obtained 2′-deoxy-D-glucopyranosidyltheophylline identical with that first obtained by Levene (*J. Biol. Chem.*, 1931, **92**, 53). Consequently they concluded that additions to glycals and acetylated glycals follow identical courses. Before publication of this result we had carried out some experiments which supported this conclusion (cf. *Chem. and Ind.*, 1949, 466).

When D-galactal was treated with 0·2% methanolic hydrogen chloride, α-methyl-2-deoxy-D-galactopyranoside (Overend *et al.*, *loc. cit.*) was obtained. The use of 3% methanolic hydrogen chloride resulted in a decreased yield of the glycoside (*i.e.*, 32% compared with 47%). Treatment of 3 : 4 : 6-triacetyl D-galactal with 2% methanolic hydrogen chloride, followed by deacetylation also yielded directly crystalline α-methyl-2-deoxy-D-galactopyranoside, thereby showing that in this instance addition of methanol to galactal and its triacetate followed the same course. However, in neither case was the reaction simple, since the glycosidic product was invariably accompanied by a liquid which is unidentified as yet. This material is optically inactive, readily absorbs bromine, and contains methoxyl residues. It would appear to be a degradation product, since it has been noticed that, as the concentration of hydrogen chloride in the methanol is increased, so the yield of liquid increases.

Experimental.

2-Deoxy-D-galactose.—D-Galactal (6·1 g.) was dissolved in ice-cold 5% sulphuric acid (85 c.c.), and the solution was kept at 0° for 24 hours. The solution was then neutralised with barium hydroxide at room temperature, and filtered through a charcoal pad. The filtrate was concentrated under diminished pressure to a syrup which was taken up in methanol (3 vols.) and set aside. 2-Deoxy-D-galactose crystallised from solution and was recrystallised from methanol in colourless cubes (4·9 g., 73%) which had m. p. 110°, $[\alpha]_D^{21}$ +57° ± 2° (equilibrium, *c*, 1·0 in water) (Found : C, 43·9; H, 7·1. Calc. for $C_6H_{12}O_5$: C, 43·9; H, 7·3%) [cf. Pigman and Isbell, *J. Res. Nat. Bur. Stand.*, 1939, **22**, 397, who give m. p. 120—121° and $[\alpha]_D$ +41° ⟶ +60·5° (equilbrium in 30 minutes; *c*, 4·0 in 0·001N-potassium hydrogen phthalate buffer); Tamm and Reichstein (*Helv. Chim. Acta*, 1948, **31**, 1630) give m. p. 105—106° and $[\alpha]_D^{18}$ +60·7° in water; Overend, Shafizadeh, and Stacey, *J.*, 1950, 671, report a 50% yield of this compound].

Potentiometric Titrations.—The following solutions were titrated potentiometrically with N-potassium carbonate : (i) 5% sulphuric acid (15 c.c.), (ii) 5% sulphuric acid (15 c.c.) containing glucal (1·4 g.) (this solution was kept for 2 hours before titration), (iii) 5% sulphuric acid (15 c.c.) containing glucal (1·6 g.) (this solution was kept at 0° for 20 hours before titration), and (iv) 5% sulphuric acid (15 c.c.) containing galactal (0·98 g.) (this solution was kept at 0° for 22 hours before titration). Results were the same in all cases.

Treatment of D-Galactal with Methanolic Hydrogen Chloride.—(a) 0·2% *Methanolic hydrogen chloride.* D-Galactal (35 g.) was treated with 0·2% methanolic hydrogen chloride (300 c.c.) at room temperature. After 1·5 hours (optical rotation constant) the solution was neutralised with silver carbonate and filtered. The filtrate was evaporated under diminished pressure, and ethyl acetate was added to the syrupy residue. Part of it crystallised and was separated. Repeated recrystallisation from ethyl acetate gave α-methyl-2-deoxy-D-galactopyranoside (19·8 g., 47%), m. p. 112—113°, $[\alpha]_D^{20}$ +170° (*c*, 0·32 in methanol) (Found : C, 47·2; H, 8·4. Calc. for $C_7H_{14}O_5$: C, 47·2; H, 7·8%) [Overend *et al.*, *loc. cit.*, give m. p. 112—113°; Tamm and Reichstein, *loc. cit.*, report m. p. 109—110°]. The syrupy material remaining was re-treated with methanolic hydrogen chloride (75 c.c.) and yielded a further amount (3·4 g.) of the above glycoside. The syrupy material finally obtained was mobile, showed no optical activity, appeared to be unsaturated, and yet contained some methoxyl residues (Found : OMe, 32%).

(b) 3% *Methanolic hydrogen chloride.* Treatment of galactal with 3% methanolic hydrogen chloride resulted in a very rapid reaction, and gave the same products, but the yield of the glycoside was reduced to 31·6%.

Treatment of Triacetyl Galactal with Methanolic Hydrogen Chloride.—3 : 4 : 6-Triacetyl galactal (5 g.) in solution in 2% methanolic hydrogen chloride (20 c.c.) was kept for 24 hours and then neutralisation was effected with silver carbonate. The silver residues were filtered off through a charcoal pad, and the filtrate was evaporated to a syrup. Distillation of this afforded a colourless mobile oil (0·6 g.), b. p. 120—130° (bath-temp.)/0·1 mm. (Found : OMe, 29·2%), which is unidentified. The still residue was dissolved in dry methanol (10 c.c.), and sodium (15 mg.) was added. After 12 hours the solution was evaporated to dryness and extracted with ethyl acetate. Evaporation of the extract afforded crystalline α-methyl-2-deoxy-D-galactopyranoside (0·5 g.), m. p. 112—113° alone or on admixture with an authentic specimen.

Our thanks are due to the British Empire Cancer Campaign (Birmingham Branch) for financial assistance. One of us (F. S.) expresses his thanks to the University of Birmingham for a scholarship from the Caroline Harrold Fund.

Chemistry Department,
The University, Birmingham, 15. [*Received, November 29th*, 1950.]

222. *Deoxy-sugars. Part XVIII. Synthesis of an Oligosaccharide by the Thermal Condensation of αβ-Methyl-2-deoxy-D-galactofuranoside.*

By W. G. Overend, F. Shafizadeh, and M. Stacey.

The nature of the product resulting from the slow distillation of αβ-methyl-2-deoxy-D-galactofuranoside has been investigated. Hydrolysis of the oligosaccharide-type material yielded 2-deoxygalactose, and methylation and hydrolysis afforded tri- and di-methyl 2-deoxygalactose.

It was noted by Deriaz *et al.* (*J.*, 1949, 2836) that on distillation of αβ-methyl-2-deoxy-L-ribofuranoside polymeric material was formed whenever superheating occurred. Similar effects were observed by Hughes, Overend, and Stacey (*J.*, 1949, 2846) with the corresponding αβ-methyl-2-deoxy-D-glucofuranoside and we now record a more extended examination of the polymeric material obtained during the purification of αβ-methyl-2-deoxy-D-galactofuranoside (Overend, Shafizadeh, and Stacey, *J.*, 1950, 671).

With Dr. R. E. Deriaz we examined the product from the thermal condensation of αβ-methyl-2-deoxy-L-ribofuranoside in somewhat closer detail. Thus the polymer was a hard colourless glass, very soluble in water but insoluble in the usual organic solvents. It was non-reducing to Fehling's solution until after acid hydrolysis. Determination of the molecular weight by the Rast method, and of the methoxyl content, indicated a polymer with about 5—7 pentose units. On treatment with methanolic hydrogen chloride there was a smooth conversion of the polymeric material into crystalline β-methyl-2-deoxy-L-ribopyranoside. It appeared that condensation of the methyl-2-deoxy-L-ribofuranoside had occurred by elimination of methanol. Qualitatively analogous results were obtained with the D-isomer of the deoxy-sugar. A detailed study was made on the more readily accessible αβ-methyl-2-deoxy-D-galactofuranoside, particularly as the condensation reaction leads to poor yields of the pure methylglycofuranoside.

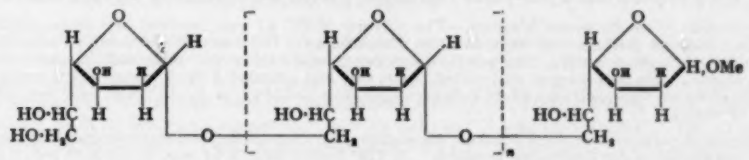
First, it was observed that if pure αβ-methyl-2-deoxy-D-galactofuranoside was subjected to rapid distillation it was not converted easily into the glassy material. Hence impurities in the crude glycoside such as traces of colloidal silver may help to induce the condensation. With this methylglycofuranoside the important fact was established that its conversion into the hard polymeric material was accompanied by the evolution of methanol. This was collected and characterised as its *p*-nitrobenzoate and by conversion into methyl salicylate. That no more fundamental change was involved than condensation by elimination of methanol was indicated by the fact that hydrolysis of the glassy material with N-hydrochloric acid at room temperature afforded 2-deoxy-D-galactose in good yield. Moreover, it was apparent that $C_{(1)}$ of the sugar is involved in the reaction since, although there was elimination of the glycosidic methyl group, the resulting glassy material was non-reducing to Fehling's solution. That the nature of the lactol ring was unchanged during the elimination of methanol could be demonstrated by comparison of the rate of hydrolysis of the polymerised material with that of the hydrolysis of methyl-2-deoxy-D-galactopyranoside. The latter was hydrolysed by N-hydrochloric acid at room temperature only after three days, whereas the glassy material was almost completely hydrolysed in thirty minutes, and αβ-methyl-2-deoxy-D-galactofuranoside in thirty minutes.

Although it is known that a methylene group at $C_{(2)}$ of the sugar renders the glycosidic centre labile (cf. Overend and Stacey, *J. Soc. Food Agr.*, 1950, **1**, 168) (especially is this so for methyl 2-deoxyglycofuranosides) and that glycals can undergo polymerisation, it is unlikely that the loss of methanol occurred between $C_{(1)}$ and $C_{(2)}$ of the deoxy-sugar to give a furanose form of galactal which then polymerised, since at no stage did absorption of bromine occur and there was no other evidence of unsaturation. Moreover, the product did not reduce hot Fehling's solution, a property typical of glycals.

Evidence obtained seems to indicate that the product of the condensation reaction is not homogeneous. For example, although it was soluble in water from which solution in some cases it could be precipitated with ethanol, a property which in the sugar series indicates polymeric character, little correlation existed between molecular weight and end-group methoxyl determinations. Also no definite stages in the reaction were observed. Values for the molecular weights varied considerably from sample to sample according to the con-

ditions used to prepare the material. Similar variable results were observed with end-group methoxyl determinations. (It was noted that the optical rotation of the material could be used as a rough guide to the molecular weight, since it became more positive the higher the molecular weight.) The molecular weight and methoxyl determinations did, however, eliminate the possibility of the material being 1 : 3-, 1 : 5-, or 1 : 6-anhydride of 2-deoxy-D-galactofuranose, or a mixture of these. From the results obtained it appears that an average of four molecules of 2-deoxy-D-galactose are joined together, although as stated considerable variation from this value was observed with some samples. In some of the deoxyribose products the almost complete absence of residual methoxyl groups could indicate substances of relatively high molecular weight.

Viscosity determinations in aqueous solution, with the viscometer described by Orthmann, Koch, and Degenfelder (*J. Amer. Leather Chem. Soc.*, 1939, **34**, 489), confirmed the oligosaccharide character of the material. In addition the material reduced lead tetra-acetate. The amount of the oxidant consumed was, for one sample, equivalent to one mole per four units of 2-deoxy-D-galactofuranose. Since this reagent is known to oxidise adjacent hydroxyl groups (Hockett and McClenahan, *J. Amer. Chem. Soc.*, 1939, **61**, 1667) it appears that such groups occur only once every four units. This could be so if four 2-deoxy-D-galactofuranose units were joined together by 1 : 5- or 1 : 6-linkages. The material was methylated by the Freudenburg technique (*Ber.*, 1938, **71**, 2505) (*i.e.*, use of sodium in liquid ammonia, followed by methyl iodide). After four methylations no further increase in methoxyl content (36·8%) occurred. The product was purified to some extent by fractional precipitation of the impurities from chloroform solution by addition of ether. The methylated product was hydrolysed by being heated at 60° with N-hydrochloric acid for 30 minutes. The hydrolysis product was fractionally distilled and some 3 : 5 : 6-trimethyl 2-deoxy-D-galactose (cf. Overend, Shafizadeh, and Stacey, *loc. cit.*) was obtained. The residues were then converted into glycosides by treatment with 1% methanolic hydrogen chloride and subsequently distilled. After repeated fractionation, two major fractions were obtained, namely, a trimethyl and a dimethyl methyl-2-deoxy-D-galactoside. No monomethyl methyl-2-deoxy-D-galactoside was detected. The trimethyl methylglycoside probably arose from incomplete hydrolysis of the methylated product or incomplete separation of the trimethyl 2-deoxy-D-galactose. Some indication was obtained that the dimethyl methylgalactoside had the primary hydroxyl group free since it yielded a syrupy toluene-*p*-sulphonyl derivative which afforded 1 mole of sodium toluene-*p*-sulphonate when heated [140° (bath-temp.) for 30 minutes] under anhydrous conditions with acetone and sodium iodide. The rapid hydrolysis of the dimethyl methyl-2-deoxy-D-galactoside (as shown by polarimetric observation) by mild acidic reagents indicated that it was a furanose.



(I.)

The results described indicate that the hard glassy material obtained when crude αβ-methyl-2-deoxy-D-galactofuranoside is distilled slowly is mainly an oligosaccharide of low molecular weight in which the units of 2-deoxy-D-galactofuranose are most probably linked through the 1 : 6-positions as shown in (I) (other products may also be present since at all stages unidentified material was obtained). It is now well established that the methylglycosides of 2-deoxy-D-galactofuranose are very labile and it would seem that the formation of this material is a further example. This is supported by the fact that α-methyl-2-deoxy-D-galactopyranoside could be heated under similar conditions for long periods and yet be recovered unchanged. Since the methylglycofuranosides of 2-deoxyribose and 2-deoxyglucose also form similar hard glassy materials when heated, it seems that this is a fairly general reaction of 2-deoxy-sugars. It is interesting to note that recently Barker and Lock (*J.*, 1950, 23) demonstrated that the anhydride derivative of ribose first reported by Bredereck *et al.* (*Ber.*, 1940, **73**, 956) is derived from two moles of ribofuranose, and Hurd and Edwards (*J. Org. Chem.*, 1949, **14**, 680) showed that thermal dehydration of α- and β-glucose leads to the formation of products having molecular weights in the di- and tri-saccharide range.

Experimental.

Experiments with 2-Deoxy-D-ribose [with R. E. Deriaz].—2-Deoxy-D-ribose (0·26 g.) was dissolved in 0·1% methanolic hydrogen chloride (5 c.c.) at 23°. The ensuing reaction was followed polarimetrically and after 12 minutes silver carbonate and silver oxide were added to arrest the reaction. The solution was filtered through a charcoal pad and then concentrated under diminished pressure. The syrupy residue was non-reducing to Fehling's solution and was αβ-methyl-2-deoxy-D-ribofuranoside (cf. Deriaz *et al.*, *loc. cit.*). On rapid heating, distillation resulted [b. p. 115—120° (bath-temp.)/0·4 mm.], but on slow heating polymerisation occurred and a hard glassy substance was formed. The glassy solid (1·214 g.) was dissolved in 1% methanolic hydrogen chloride. After 0·5 hour the specific rotation of the solution was constant. The solution was neutralised with barium carbonate and filtered. After removal of the solvent by evaporation at 40°, the residue was extracted with benzene. Evaporation of the benzene at 40° gave β-methyl-2-deoxy-D-ribopyranoside (0·36 g.), m. p. 83·5° alone or on admixture with an authentic specimen.

2-Deoxy-D-galactose.—2-Deoxy-D-galactose, prepared by the method already reported (Overend, Shafizadeh, and Stacey, *J.*, 1950, 671), showed m. p. 110° and $[\alpha]_D^{20}$ +57° ± 2° (equilibrium, *c*, 1·0 in water).

αβ-Methyl-2-deoxy-D-galactofuranoside.—To 2-deoxy-D-galactose (3·8 g.) in methanol solution (100 c.c.), 4·5% methanolic hydrogen chloride (1 c.c.) was added. The reaction was followed polarimetrically and at the maximum lævorotation the solution was neutralised with silver carbonate. The glycoside (3·5 g.) was isolated in the usual manner. It showed n_D^{21} 1·4828 and $[\alpha]_D^{17}$ −68° (*c*, 0·67 in methanol) (Found: OMe, 17·7. Calc. for $C_7H_{14}O_5$: OMe, 17·4%). On rapid distillation of this crude material a colourless syrup was obtained, b. p. 180° (bath-temp.)/0·001 mm., $[\alpha]_D^{17}$ −75° (Found: OMe, 17·6%).

α-Methyl-2-deoxy-D-galactopyranoside.—This was prepared according to Overend, Shafizadeh, and Stacey (*loc. cit.*), and had m. p. 112—113°, $[\alpha]_D^{18}$ +164° (*c*, 0·38 in methanol) (Found: OMe, 17·8. Calc. for $C_7H_{14}O_5$: OMe, 17·4%).

Formation of the Polymer.—αβ-Methyl-2-deoxy-D-galactofuranoside (5 g.) was heated at 230° (bath-temp.)/12 mm. for 15 minutes. A colourless mobile liquid was evolved and collected in a trap cooled with liquid air. This mobile liquid was identified as methanol and further characterised as its *p*-nitrobenzoate, m. p. 96° alone or on admixture with an authentic specimen. The residue was further heated at 210—230°/12 mm. for 2·5 hours and then any unchanged material or anhydride was removed by distillation [up to 235° (bath-temp.)/0·01 mm.]. The polymer was a brittle glass, soluble in water, but less so in ethanol. The above example is a typical procedure, although it should be recorded that the degree of polymerisation obtained is greater for lower pressures. The optical rotation became increasingly positive the greater the degree of polymerisation. For the largest polymer obtained $[\alpha]_D^{18}$ was +11·4° (*c*, 1·73 in water). Molecular-weight determinations (cryoscopic) on several samples indicated that the polymers ranged on an average from 4 to 8 units. Methoxyl determinations supported the molecular-weight data although in general they tend to give slightly lower values. Thus a polymer with molecular weight 650 (corresponding to 4—5 units) showed OMe, 3·4%. This polymer was not precipitated by ethanol (2 vols.), but more highly polymerised specimens showing traces only of methoxyl content could be precipitated from aqueous solution by addition of one volume of ethanol. When dried, this precipitate was a pale yellow hygroscopic powder, non-reducing to Fehling's solution.

Hydrolysis of the Polymeric Material.—The polymer (0·537 g.) was dissolved in N-hydrochloric acid (10 c.c.) and the solution was kept at room temperature. The reaction, followed polarimetrically, was complete in 30 minutes. The solution was neutralised with silver oxide and filtered through a charcoal pad. The filtrate was evaporated to dryness and afforded a thick syrup which crystallised. Recrystallisation from methanol afford 2-deoxy-D-galactose (0·325 g.), m. p. 110°, $[\alpha]_D^{20}$ +58° (equilibrium, *c*, 1·0 in water).

Attempt to polymerise α-Methyl-2-deoxy-D-galactopyranoside.—α-Methyl-2-deoxy-D-galactopyranoside (1 g.) was heated under diminished pressure. At 170° (bath-temp.)/0·01 mm. it began to reflux and no methanol was evolved. After 45 minutes at this temperature the starting material was recovered unchanged.

Methylation of the Polymer.—The polymer (powder form) (3 g.) was smoothly methylated by dissolving it in liquid ammonia (250 c.c.) and adding excess of sodium (1·5 g.) in small pieces, followed by methyl iodide (15% excess, 12 g.). The procedure was repeated 4 times, and then the liquid ammonia was allowed to evaporate and the residue was extracted repeatedly with chloroform. The extract was dried ($MgSO_4$) and evaporated to dryness. The syrupy residue was dissolved in chloroform (15 c.c.) and ether (30 c.c.) was added. A tarry material separated and was removed. Evaporation of the solvent gave a syrupy material (2·3 g.), insoluble in water and non-reducing to Fehling's solution, $[\alpha]_D^{19}$ ±0° (*c*, 1·3 in ethanol) (Found: OMe, 36·8%).

Hydrolysis of the Methylated Product.—The purified methylated polymer (2·32 g.) and N-hydrochloric acid (15 c.c.) were heated to 60° for 0·5 hour and then left for 20 hours at room temperature. The solution was neutralised with silver carbonate and filtered through a charcoal pad, and the filtrate was evaporated to dryness under diminished pressure. A pale brown mobile syrup (2·0 g.) was obtained, which reduced Fehling's solution.

Fractionation of the Hydrolysis Product.—The syrupy material was distilled and the distillate was mainly a trimethyl 2-deoxy-D-galactofuranoside (see table, fraction *A*) which was purified by successive redistillation. The still residues were combined and treated with 1% methanolic hydrogen chloride (15 c.c.) for 5 hours to effect glycosidation. The solution was neutralised with silver carbonate and

filtered through a charcoal pad, and the filtrate evaporated to dryness. The syrupy residue was fractionally distilled (see table) and the fractions obtained were further purified by repeated redis-

Fractionation products.

Fraction.	OMe, %. Found.	Calc.	n_D.	B. p./mm.	Weight (mg.).	Ref.
A, Trimethyl 2-deoxy-D-galactose	46·7	45·1	1·4460	90°/0·3	200	1
B, Trimethyl methyl-2-deoxy-galactoside	53·5	56·3	1·4420	83°/0·01	310	2
C, Dimethyl methyl-2-deoxy-galactoside	44·9	45·1	1·4561	110°/0·05	606	—
D, Residue from redistillations of *C*	—	—	—	—	82	—
Tarry still residue	—	—	—	—	252	—

[1] Overend, Shafizadeh, and Stacey (*loc. cit.*) give b. p. 105—110° (bath-temp.)/0·001 mm. for 3 : 5 : 6-trimethyl 2-deoxygalactofuranose. [2] *Idem, ibid.*, quote b. p. 130—135° (bath-temp.)/12 mm., n_D^{21} 1·4421, for 3 : 5 : 6-trimethyl $\alpha\beta$-methyl-2-deoxygalactofuranoside.

tillation. This process yielded three main fractions, namely, trimethyl 2-deoxy-D-galactose (*A*), trimethyl methyl-2-deoxygalactoside (*B*) (Found : C, 54·3 : H, 9·4. Calc. for $C_{10}H_{20}O_5$: C, 54·6; H, 9·1%), dimethyl methyl-2-deoxygalactoside (*C*), and some residues which were hard tarry materials after heating at 140°/0·02 mm. No monomethyl methyl-2-deoxy-D-galactoside was detected.

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[*Received, November 29th*, 1950.]

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223. *The Alkalimetric Determination of Metals with the Aid of Acid–Base Indicators.*

By J. F. COETZEE.

This paper deals with the determination of aluminium, cadmium, and cobalt by titration with standard alkali. Completion of precipitation of the metallic hydroxide is determined with the aid of a suitable acid–base indicator. Similarly, free mineral acid may be titrated in the presence of these metals by use of an indicator of proper pH range. This principle has now been applied for the first time to the determination of cobalt. Bayer's procedure for the determination of aluminium has been substantially modified, and a new one proposed for cadmium.

Principle of Method.—During an attempt to develop new adsorption-indicator methods for the determination of phosphates, the possibility arose of estimating metals by alkalimetric titration. With this object, a series of experiments was conducted to find which adsorption indicators would be useful for the alkalimetric determination of those metals which form insoluble phosphates, such as lead and aluminium, and alizarin-red S was investigated. On titration of an aluminium chloride solution with sodium hydroxide in the presence of this compound, a pronounced colour change was observed; however, it was found that this change was not connected with adsorption phenomena, but that the dye merely responded to change in pH, behaving as an acid–base indicator. Hence, it seemed feasible to determine aluminium by first titrating the free mineral acid content of its solutions with the aid of an acid–base indicator of pH range sufficiently low to exclude possible precipitation of aluminium hydroxide, followed by the titration of aluminium by employing an indicator of higher pH range. It was then found that Bayer (*Z. anal. Chem.*, 1885, **24**, 542) had used a similar method for aluminium, but under his conditions, it was tedious and not of great accuracy; also, Carrière, Guiter, and Portal (*Bull. Soc. chim.*, 1946, **13**, 99) had applied the principle to cadmium. However, the wide scope of the method does not appear to have been realized, and it has now been extended to the determination of cobalt with satisfactory results, and further extensions are being examined, particularly to copper, antimony, zinc, mercury, and lead.

Determination of Free Mineral Acid Content of Metal-salt Solutions.—(a) *Relation between activity of metallic ions and their "hydroxide precipitation* pH *value."* Although the addition of bases to metal-salt solutions rarely leads to the precipitation of simple hydroxides, it is nevertheless evident from electrometric studies that the conditions under which precipitation occurs are largely governed by the usual solubility-product relations pertaining to the pre-

cipitation of simple hydroxides (Britton, *Ann. Reports*, 1943, **40**, 43). Consider the precipitation of the hydroxide of a bivalent metal: $a_{M^{++}}a^2_{OH^-} = L$, where a denotes ion activity and L solubility product. A ten-fold decrease in the value of $a_{M^{++}}$ will result in a ten-fold increase in that of $a^2_{OH^-}$, or about a three-fold increase in a_{OH^-}, corresponding to an increment in the "hydroxide precipitation pH value" of approximately 0·48 unit. This value for a tervalent metal is less susceptible to the activity factor, a ten-fold decrease in the value of $a_{M^{+++}}$ resulting in a rise of only *ca.* 0·33 unit. This dependence of the hydroxide precipitation pH value of a metal upon the activity of its ions has an important bearing upon the determination of the free mineral acid content of metal-salt solutions.

(b) *Selection of indicator.* The particular indicator selected for the determination of the free mineral acid content of such solutions should comply with two primary requisites. First, its colour transformation should occur at a pH value lower than that at which precipitation of the metal commences, which in turn is determined by the nature of the metal and the activity of its ions in the particular solution. The nature of the anions present normally exerts but little effect upon the magnitude of the hydroxide precipitation pH value (Britton, *J.*, 1925, **127**, 2112, 2143) unless complex-ion formation occurs, as with, *e.g.*, mercury and cadmium. Secondly, the indicator selected should have a transformation interval sufficiently high to permit of a well-defined colour change in conjunction with alkali of the particular concentration employed. In practice, any of the recommended indicators (see, *e.g.*, Kolthoff and Rosenblum, "Acid–Base Indicators," Macmillan, N.Y., 1937) showing changes between pH 2 and 12 may be employed in conjunction with N-titrants without introducing very serious errors. With 0·1N-titrants the latitude permissible is reduced to 3—11, and with 0·01N-titrants to 4—10; in certain instances the use of indicator mixtures (*op. cit.*; Kolthoff, *Biochem. Z.*, 1927, **189**, 26) is preferable.

Finally, certain secondary considerations arise, such as the colour of the solution titrated, and the possibility of determining both acid and metal in the same aliquot portion of solution.

(c) *Electrometric determination of hydroxide precipitation* pH*-values.* Britton (*Ann. Reports, loc. cit.*) has summarised all available electrometrically determined hydroxide precipitation pH values; those of present interest were reported as follows for 0·02M-solutions: $Hg(NO_3)_2$, 2; $HgCl_2$, 7·3; Al, 4·1; Cu, 5·3; Pb, 6·0; $CdSO_4$, 6·7; $CdCl_2$, 7·6; Co, 6·8; Zn, 6·8—7·1. The author's results are in good agreement with these data.

Precipitation of Metallic Hydroxides.—(a) *Composition of metallic "hydroxides."* The composition of the precipitate produced by gradual addition of alkali to a metal-salt solution depends upon a variety of factors, the more important in the present connection being (i) temperature; (ii) concentration of the titrant and solution, as well as mode of addition of the former and agitation of the latter; (iii) nature of the anions present; (iv) the particular pH value at which the titration has been terminated.

It has been well established that gradual addition of alkali to metal-salt solutions generally results at first in precipitation of basic salts, silver being one of the very few exceptions (Britton, *Ann. Reports, loc. cit.*). The stability of these basic salts is of fundamental importance in the application of the principle of alkalimetric titration to any particular metal. The author's results with the aid of acid–base indicators clearly indicate that the order of stability of the more usual basic salts is sulphate > chloride > nitrate. In all instances investigated, the basic nitrates could be quantitatively transformed into the corresponding hydroxides by a rise in pH and temperature; under similar conditions the corresponding basic chlorides were often incompletely decomposed, and certain basic sulphates proved sufficiently stable to serve as a basis for the quantitative alkalimetric determination of the metal in question; for instance, a procedure could be developed for the determination of copper, depending upon the remarkable stability of the basic sulphate $3CuO,CuSO_4,aq$.

(b) *Quantitative precipitation of metallic hydroxides.* Consider the precipitation of the "hydroxide" of a z-valent metal:

$$a_M a^z_{OH^-} = L$$

i.e., $$a_{OH^-} = (L/a_M)^{1/z}$$

or $$a_{H^+} = K_w(a_M/L)^{1/z} = Ka_M^{1/z}$$

From this it follows that an increase of one unit in pH should reduce a_M to 10^{-z} of its original value. With a tervalent metal, such as aluminium, this will correspond to precipitation of 99·9% of the metal. Even with a bivalent metal, a rise in pH value of 2 units should suffice to ensure practically quantitative precipitation.

However, since alkalimetric titration of metals generally results at first in precipitation of basic salts, and not of simple hydroxides, a rise in pH value of even 2 units is insufficient to precipitate the metal quantitatively as hydroxide. The results obtained indicate that in general an increase in pH value of 2·5—3 units, in conjunction with an adequate rise in temperature, is required in order to effect this conversion quantitatively. Only with metals such as copper, where the final stable compound produced is itself a basic salt, is a smaller rise in pH value sufficiently effective for analytical purposes.

(c) *Requisites for a successful alkalimetric procedure.* Any satisfactory alkalimetric procedure should conform to certain requirements, the more important of which are: (i) The results should be independent, over a sufficient range, of the concentration, which not only determines the magnitude of the solubility error introduced, but also exerts a profound influence on the composition of the precipitate produced; (ii) once quantitative formation of the ultimate product has been accomplished, the results should be independent of moderate variations in temperature; (iii) similarly, this final product must also be sufficiently immune to further increase in pH, in order to permit of the satisfactory application of an acid–base indicator; (iv) the degradation of any unstable basic salt into the ultimate stable product should take place with sufficient rapidity, and this should be accomplished within the pH and temperature range attainable during ordinary acid–base titrations.

Determination of Aluminium.—(a) Bayer (*loc. cit.*) employed sufficient N-sodium hydroxide solution to redissolve the initially precipitated aluminium hydroxide. One aliquot portion of the resulting solution was then titrated with N-sulphuric acid and litmus (pH 5·0—8·0), and another with the same acid and tropæolin-OO (1·3—3·2), the difference being calculated as alumina. This procedure is obviously unsound. At the litmus end-point, appreciable dissolution of aluminium hydroxide as sulphate will already be taking place, resulting in an ill-defined colour change. Further, the pH range of tropæolin-OO is so low that this indicator is not sufficiently responsive to titrants of N-concentration. Cross and Bevan (*J. Soc. Chem. Ind.*, 1889, **8**, 252) replaced litmus by phenolphthalein (pH 8·0—9·8), and tropæolin-OO by methyl-orange (3·1—4·4), but (see p. 1001) the latter indicator is unsatisfactory. Similarly, the use of alizarin-red S instead of methyl-orange (Sabalitschka and Reichel, *Arch. Pharm.*, 1925, **263**, 193) is not to be recommended, since solution of aluminium hydroxide is still incomplete at the pH represented by the end-point of this indicator (pH 4·0—6·0). The use of fluoride and oxalate in order to form complex ions has also been recommended (see p. 1001).

The author prefers to determine the free mineral acid content of aluminium solutions by direct titration with the aid of screened dimethyl-yellow (see p. 1002). This procedure is rapid and accurate.

The determination of acid and aluminium in conjunction has been a subject of much controversy. Schmatolla (*Ber.*, 1905, **38**, 1, 985) conducted his titrations at a high temperature in order to avoid formation of basic salts, and used alkali carbonate as titrant. Scott (*J. Ind. Eng. Chem.*, 1915, **7**, 1059) recommended the titration of relatively concentrated solutions at a high temperature, using carbonate-free alkali as titrant. Sutton ("A Systematic Handbook of Volumetric Analysis," 1935) advocated the titration of relatively dilute solutions at room temperature.

It has now been found that titrations conducted at room temperature to the phenolphthalein end-point invariably yield low results, presumably on account of basic salt formation. If, however, an indicator of higher pH range is employed, or phenolphthalein is used at a high temperature, ill-defined, transient end-points are obtained, probably owing to aluminate formation. The circumventing of these difficulties is described on p. 1002.

(b) *Composition of aluminium "hydroxide" precipitates.* The composition of the precipitate produced by gradual addition of alkali to aluminium solutions has been studied by many investigators, chiefly by means of two methods, *viz.*, conductometric and electrometric, but the results obtained are not concordant, though on the whole they indicate the existence of definite basic salts at ordinary temperatures. For instance, Robinson and Britton (*J.*, 1931, 2817) concluded from their conductometric studies that "maximum insolubility" of the precipitate produced from aluminium sulphate solutions corresponded to the consumption of 5·76 equivs. of alkali, a value in good agreement with the electrometrically determined one of 5·70 equivs. (Britton, *J.*, 1925, **127**, 2120). On the other hand, Kanning and Kratli (*Ind. Eng. Chem. Anal.*, 1933, **5**, 381), employing the antimony electrode in aluminium chloride solutions, reported a value of exactly 6 equivs. According to these authors, the presence of 1% of sodium sulphate led to an under-titration error of 1·5%. These results support the contention that the basic sulphates are generally more stable than the

corresponding chlorides; they are essentially in harmony with those obtained by the author with the aid of acid–base indicators.

Determination of Cadmium.—Composition of precipitate. Attempts to determine the composition of the precipitate produced at room temperature by gradual addition of alkali to cadmium solutions have been carried out by application of three different methods, *viz.*, electrometric (Britton, *J.*, 1925, **127**, 2152; *Ann. Reports, loc. cit.*) and conductometric (Harned, *J. Amer. Chem. Soc.*, 1917, **39**, 252) analysis, and a method due to Pickering (*J.*, 1907, **91**, 1981), which has been developed by Carrière *et al.* (*loc. cit.*). The results obtained by the first two methods pointed to the existence at room temperature of a definite basic sulphate, $3Cd(OH)_2,CdSO_4,aq$. Pickering's investigations, carried out with the aid of pH indicators, merit closer attention. He attempted to follow the alkalimetric precipitation of cadmium with the aid of phenolphthalein (pH 8·0—9·8) and found that even very gradual addition of alkali resulted in almost instantaneous production of a pink colour. He noted, however, that this was due to the precipitate's turning pink, whereas the supernatant liquid remained colourless. This phenomenon was also observed by the author, and it is hoped that a systematic investigation of the adsorption characteristics of cadmium "hydroxide" precipitates may lead to the development of an adsorption-indicator method for the determination of this metal (cf. cobalt).

It is shown (p. 1002) that quantitative formation of cadmium hydroxide can only be accomplished by conducting the titration at a high temperature. Further, the pH range of phenolphthalein is too low to permit of the quantitative precipitation of cadmium hydroxide at any temperature. Consequently, the precipitate obtained by Pickering was probably an indefinite mixture of basic salts, and his finding that "permanent alkalinity to phenolphthalein" corresponded to the consumption of 1·462 equivs. of alkali is of little analytical importance. Carrière *et al.* (*loc. cit.*) titrated cadmium sulphate solutions with sodium hydroxide to the thymolphthalein end-point, and deduced the formation of the basic sulphate, $3Cd(OH)_2,CdSO_4,aq$.

Determination of Cobalt.—(a) *Composition of precipitate.* The blue precipitate produced at room temperature by addition of excess of alkali to cobalt solutions changes on heating into a rose-coloured compound, which in turn is gradually converted into a brown one by prolonged heating and exposure to the atmosphere. The composition of these precipitates has been a subject of considerable controversy (Hantzsch, *Z. anorg. Chem.*, 1912, **73**, 304; Stillwell, *J. Physical Chem.*, 1929, **33**, 1247; Hüttig and Kassler, *Z. anorg. Chem.*, 1930, **16**, 24; Weiser and Milligan, *J. Physical Chem.*, 1932, **36**, 722). The modern view, based upon evidence from *X*-radiograms, indicates that both the blue and the rose precipitate are crystalline, differing merely in form. The blue α-hydroxide is relatively unstable, and its conversion into the rose β-variety is aided by increase in alkalinity and rise in temperature, and retarded by the presence of cobalt ions. Both varieties are represented by $Co(OH)_2$.

The procedure developed for the alkalimetric determination of cobalt depends upon the production of the rose β-hydroxide. Its solubility is sufficiently low to permit of practically quantitative precipitation of the metal, even from very dilute solutions (Curtman and John, *J. Amer. Chem. Soc.*, 1912, **34**, 1684; Almkvist, *Z. anorg. Chem.*, 1918, **103**, 240; Britton, *J.*, 1925, **127**, 2117). Atmospheric oxidation of the moist β-hydroxide gives rise to a brown compound, presumably $Co(OH)_3$. Even though this transition takes place without the consumption of additional alkali, $2(CoO,H_2O) + O + H_2O \longrightarrow Co_2O_3,3H_2O$, it should nevertheless be avoided as far as possible, since the colour change of the indicator is largely masked by the presence of appreciable amounts of the brown hydroxide. It is shown (p. 1003) that, with care, atmospheric oxidation of the rose hydroxide may be reduced to negligible proportions, and a well-defined colour change ensured. Only on excessive boiling does the rose colour of the β-hydroxide change into a dirty brown and even then this transition is relatively slow.

Ammonium salts must be rigidly excluded, both because of their solvent action upon cobalt hydroxide to form complex ammines, and because of their reaction with alkali at the relatively high pH value required for quantitative precipitation of cobalt. Cyanides, tartrates, citrates, and glycerol also exert a solvent action upon cobalt hydroxide (Mellor, "A Comprehensive Treatise on Inorganic and Theoretical Chemistry," 1946, Vol. 14, 567), and must therefore be absent during the alkalimetric determination of this metal. On the other hand, the possibility exists that a suitable reagent could be deliberately added in order to maintain cobalt in solution during the alkalimetric determination of some other metal in admixture, but obviously such an addition should not affect the acidity of the solution (cf. Wagner, *Z. anal. Chem.*, 1933, **95**, 311).

The electrometric titration of cobalt solutions at room temperature (Britton, *loc. cit.*;

Britton and Robinson, *Trans. Faraday Soc.*, 1932, **28**, 531) provided evidence for the existence of definite basic salts, such as $7Co(OH_2),CoCl_2,aq.$, corresponding to the consumption of 1·75 equivs. of alkali, and Pickering (*loc. cit.*) found that " permanent alkalinity to phenolphthalein " corresponded to the consumption of 1·518 equivs. of alkali but his precipitate was probably a mixture of basic salts, as with cadmium (p. 1000).

Experimental.

Free Mineral Acid Content of Metal-salt Solutions.

Aluminium.—On account of the relatively low hydroxide precipitation pH value of aluminium, determination of the free mineral acid content of its solutions necessitates careful control of experimental conditions. The titrations should be conducted slowly, since the hydroxide which is locally precipitated as each drop of basic titrant enters the solution redissolves with difficulty. For optimum results the concentration of the aluminium solution should not exceed approximately 0·03M., and the titration should not be continued further than to about pH 3·3, owing to the ease with which local precipitation of the hydroxide occurs in the more immediate vicinity of its true precipitation pH value. Titrations terminated at pH 3·3 require the use of titrants of at least N-concentration. The only simple indicator for this purpose is *p*-sulphobenzeneazobenzylaniline (pH 1·9—3·3), which affords a moderate degree of accuracy provided the titration is continued to its yellow alkaline extreme. A greatly improved end-point and more accurate results can be obtained with the aid of the dimethyl-yellow–methylene-blue " screened " indicator for pH 3·3 (Kolthoff and Rosenblum, *op. cit.*).

Titrations carried out with 0·1N-alkali can only be conducted satisfactorily if the aluminium is first converted into a complex fluoride (Craig, *J. Soc. Chem. Ind.*, 1911, **30**, 185; Scott, *loc. cit.*) or oxalate (Sutton, *op. cit.*). An approximation to the true titration value can be obtained by slowly titrating the dilute solution, at concentrations not greater than 0·005M. with regard to aluminium, with the aid of the methyl orange–xylene cyanol FF indicator for pH 3·8 (Hickman and Linstead, *J.*, 1922, **121**, 2502). In this titration, premature precipitation of aluminium hydroxide is not easily avoided, and the colour transformation is not clearly defined. None of the indicators hitherto advocated, *viz.*, tropæolin-OO (Bayer, *loc. cit.*), methyl-orange (Cross and Bevan, *loc. cit.*), and alizarin-red S (Sabalitschka and Reichel, *loc. cit.*, is even moderately satisfactory for this purpose.

Cadmium.—The determination of free mineral acid in the presence of cadmium is very simple. The hydroxide precipitation pH value of this metal is relatively high, and its ions are colourless. Furthermore, since cadmium ions combine with halide ions to form complex anions, resulting in a decrease in $a_{Cd^{++}}$ (Moeller and Rhymer, *J. Physical Chem.*, 1942, **46**, 477), precipitation of the hydroxide may be retarded until even higher pH values have been attained (Bersch, *Z. physikal. Chem.*, 1891, **8**, 392; Britton, *locc. cit.*). Experiments to be reported later show that addition of a halide salt retains cadmium in solution during the alkalimetric determination of some other metals in admixture.

Even in the absence of halide ions, a wide variety of indicators is available for the determination of free mineral acid in the presence of cadmium. Titration of relatively concentrated cadmium solutions with N-alkali is best conducted with the aid of dimethyl-yellow (pH 2·9—4·0) or bromophenol-blue (pH 3·0—4·6). For more dilute solutions titrations with 0·1N-alkali may be safely continued to the end-points of α-naphthyl-red (pH 3·7—5·0), bromocresol-green (3·8—5·4), and even methyl-red (4·4—6·3). A mixed indicator for the range 4·4—6·0 (B.D.H.) gives excellent results.

Cobalt.—Here, again, owing to the comparatively high hydroxide precipitation pH value of this metal, the procedure is simple. However, the colour of cobalt ions in solution interferes with the colour of the indicator in solutions of high cobalt content, and for optimum results the solution should be diluted to approximately 0·02M. This dilution has the additional effect of displacing the hydroxide precipitation pH to even higher values, thereby permitting the use of indicators of correspondingly higher range. Further, a colour change to blue or violet is more easily visible in the pink cobalt solution than one to red, yellow, or green, and bromocresol-purple (pH 5·2—6·8) is recommended. The free mineral acid content of cobalt solutions can also be determined at higher temperatures with the aid of this indicator, a fact which has an important bearing upon the determination of copper and cobalt in admixture (to be reported later).

Determination of Certain Metals in Salt Solutions.

Aluminium.—An approximately 0·03M-aluminium nitrate solution was titrated at room temperature by 0·1N-carbonate-free sodium hydroxide solution, with the aid of various indicators. The results are summarised below.

Theoretical titre : 43·87 ml.

Titration no.	Indicator.*	Range : pH units.	Titre, ml.	Nature of colour change.
1	B.T.B.	6·0— 7·6	42·2—43·2	Very gradual
2	C.R.	7·0— 8·8	43·2—43·7	Less gradual, but still ill-defined
3	P.P.	8·0— 9·8	43·6—43·8	Defined to 0·2 ml.
4	T.P.	9·3—10·5	44·5— ?	Fleeting

* The following abbreviations are employed for frequently used indicators : methyl-orange, M.O.; bromophenol-blue, B.P.B.; bromocresol-green, B.C.G.; methyl-red, M.R.; bromocresol-purple, B.C.P.; bromothymol-blue, B.T.B.; phenol-red, P.R.; *o*-cresol-red, C.R.; thymol-blue, T.B.; phenolphthalein, P.P.; thymolphthalein, T.P.

It was evident from the very gradual colour change obtained in titration no. 1 that the precipitate was still absorbing alkali over the pH range 6·0—7·6. Titration no. 2 illustrated how an indicator of higher range afforded a sharper colour change. The P.P end-point, titration no. 3, was still better and corresponded fairly closely to the titre theoretically required for the formation of aluminium hydroxide; however, the end-point lacked definition and brilliance, and its rapid fading rendered it unsuitable for any but approximate determinations. This fading of the P.P. end-point was apparently caused by the gradual redissolution of the hydroxide as aluminate, a process more clearly illustrated by the extremely sluggish development of the T.P. end-point in titration no. 4.

These results indicate that degradation of the unstable basic nitrates of aluminium into the hydroxide must be nearly complete at the lower limit of the pH range of phenolphthalein; however, production of a permanent end-point is being prevented, probably on account of aluminate formation. Any attempt to develop an alkalimetric method for the determination of aluminium should allow for these two facts.

These difficulties have been overcome by addition to the solution of sufficient nitrobenzene to protect the aluminium hydroxide precipitate from the influence of excess of hydroxyl ions. This principle is analogous to that applied by Caldwell and Moyer (*Ind. Eng. Chem. Anal.*, 1935, **7**, 38) to render silver chloride precipitates immune against attack by thiocyanate ion in the Volhard titration; according to them, the nitrobenzene causes the silver chloride to be drawn to the interface and thus removes it from the aqueous phase. It does not necessarily follow that the "covering up" of aluminium hydroxide precipitates by nitrobenzene depends upon exactly the same principle; nevertheless, both silver chloride and aluminium hydroxide precipitates are characterised by their powerful adsorption capacity, and this may account for their analogous behaviour with nitrobenzene.

The phenolphthalein end-point under these conditions is well-defined, brilliant, and remarkably permanent, and permits of the titration of aluminium solutions with a high degree of accuracy. It is immaterial whether the nitrobenzene is present from the commencement of the titration, or whether it is added just before the end-point. Consequently, its tendency to "cover up" basic aluminium salts must be considerably less pronounced than it is for the normal hydroxide. Excessive amounts of nitrobenzene do no harm, except that unduly high concentrations of indicator must be employed.

A series of titrations conducted on this basis clearly indicated that quantitative formation of of aluminium hydroxide can only be effected from hot solutions. Titration at room temperature invariably yields low results, the under-titration error depending upon the anions present: sulphate > chloride > nitrate. Quantitative conversion of the basic nitrates into the hydroxide is easily effected by conducting the titration above 70°. The corresponding chlorides are considerably more stable, but may nevertheless be quantitatively decomposed by adding the alkali slowly to the boiling solution. The under-titration error caused by the presence of sulphate ions can only be avoided if these are first removed by addition of excess of barium nitrate solution. The resulting barium sulphate need not be removed, since it is immune to attack by hydroxyl ions over the entire pH range covered during ordinary acid–base titrations.

Nitrobenzene, being volatile in steam, should only be used at room temperature. The following procedure is therefore recommended: (*a*) An approximation to the true titration value is obtained by titration at room temperature to the phenolphthalein end-point, by use of 2—3 ml. of nitrobenzene per 0·1 g. of aluminium present and 10—15 drops of 0·1% phenolphthalein solution per 100 ml. of liquid present at the end-point. (*b*) The titration is conducted in boiling solution to the stage corresponding to (*a*), the liquid cooled, the nitrobenzene and phenolphthalein added, and the last few drops of alkali introduced at room temperature. The results obtained by this procedure are summarised in the following table.

Standard solutions of aluminium nitrate were prepared as follows: Aluminium sheet (C.P.; supplied by the South African Bureau of Standards) was dissolved in 10% sodium hydroxide solution, the aluminium precipitated as hydroxide by addition of N-nitric acid, and the hydroxide just dissolved by further addition of acid. A slight excess of acid of appropriate concentration, just sufficient to ensure a practicable titration value, was then added, and the solution boiled for several minutes, cooled, and made up to the desired volume.

Free mineral acid was titrated with the aid of "screened" dimethyl-yellow when N-alkali was used, and of fluoride when 0·1N-titrant was required. Two solutions of carbonate-free sodium hydroxide were standardised against Merck's *pro analysi* potassium hydrogen phthalate and found to be 1·004N. and 0·1202N. All aluminium solutions were titrated in 25-ml. portions.

Al, g.-ions per l.	Acid, ml.	Acid + Al, ml.	Al, ml. Found.	Al, ml. Calc.	Error, ml.	Al, g.-ions per l.	Acid, ml.	Acid + Al, ml.	Al, ml. Found.	Al, ml. Calc.	Error, ml.
0·4083	11·23	41·69	30·46	30·51	−0·05	0·04072	10·62	35·94	25·32	25·40	−0·08
0·3536	8·35	34·73	26·38	26·42	−0·04	0·03469	6·34	27·98	21·64	21·64	±0
0·3028	10·40	33·08	22·68	22·62	+0·06	0·03283	7·54	28·00	20·46	20·48	−0·02

Cadmium.—Standard solutions of cadmium nitrate were prepared from C.P. metal (Coleman and Bell). Titration of these solutions at room temperature with the aid of phenolphthalein (8·0—9·8) and thymolphthalein (9·3—10·5) gave low results, and the fact that the titre was not independent of the concentration precluded any possibility of developing a quantitative procedure on this basis. Consequently, an attempt was made to effect quantitative conversion of the basic salts into the hydroxide by heat. Even under these conditions the phenolphthalein end-point corresponded to slight under-titration, but this error could be entirely eliminated by the use of thymolphthalein as indicator. All titrations were conducted at temperatures above 70°, 2 ml. of a 0·05% thymolphthalein solution in

70% alcohol being used per 100 ml. of liquid present at the end-point. The proper " blank " corrections were evaluated and applied. The results obtained by this procedure are given below.

Cd, g.-ions per l.	Vol. titrated, ml.	Alkali used, N.	Acid, ml.	Acid + Cd, ml.	Blank, ml.	Acid + Cd, ml. (corr.).	Cd, ml. Found.	Cd, ml. Calc.	Error, ml.
0·5002	20	1·004	3·73	23·68	0	23·68	19·95	19·94	+0·01
0·5007	20	1·004	5·35	25·27	0	25·27	19·92	19·95	−0·03
0·04980	20	0·1202	2·86	19·54	0·08	19·46	16·60	16·58	+0·02
0·05005	20	0·1202	3·45	20·17	0·08	20·09	16·64	16·65	−0·01
0·01003	100	0·1202	2·62	19·53	0·23	19·30	16·68	16·68	0
0·009997	100	0·1202	4·89	21·72	0·23	21·49	16·60	16·63	−0·03

Anion effect. The influence of halide ions has already been referred to (p. 1001). Although the presence of a halide salt may be useful during the determinations of the free mineral acid content of cadmium solutions, as well as during the alkalimetric determination of some other metal in admixture with cadmium, yet it should be absent if cadmium itself is to be titrated. Similarly, sulphate ions must also be absent, but for a different reason. The comparative stability of the basic sulphates of cadmium precludes a well-defined colour change with any available acid–base indicator. The nearest approach to ideal behaviour is afforded by thymolphthalein (9·3—10·5). If the titration is conducted at a normal rate, a transient end-point is obtained, indicating that the precipitate is still absorbing alkali over the indicator pH range. If, however, the titrant is added sufficiently slowly, time being allowed for the repeated reversal of the colour change, the titre corresponding to quantitative formation of cadmium hydroxide can be approached closely. Although this procedure is too tedious for analytical purposes, it indicates that quantitative conversion of the basic sulphates of cadmium into the hydroxide may be accomplished at high temperatures provided a sufficiently high pH value can be attained. According to Carrière *et al.* (*loc. cit.*), the titration curve of cadmium sulphate by sodium hydroxide shows inflections at pH 9·0—10·6 and 11·2—12·8 due, respectively, to formation of $3Cd(OH)_2,CdSO_4,aq.$ and its conversion into hydroxide. They base a method for determination of cadmium on titration of its sulphate to the basic stage by use of thymolphthalein.

With available acid–base indicators, the conversion into hydroxide cannot be effected sufficiently rapidly: titrations conducted with N-alkali may theoretically be continued up to about pH 11, but the pH values attainable with indicators are considerably lower. None of those indicators of higher pH range than thymolphthalein (9·3—10·5) is even moderately satisfactory for volumetric analysis, and several of these, including alizarin-yellow (10·1—12·1) are so rapidly precipitated by metal ions that they are useless for the alkalimetric determination of metals. This method would be of much wider utility if suitable indicators were available for the pH range 10—12. The alkalimetric titration of cadmium should therefore be conducted either to the basic sulphate stage as above or in the absence of sulphate ions; these should be precipitated by addition of chloride-free barium nitrate solution in excess, and cadmium determined directly in the presence of the resulting precipitate (cf. aluminium).

Cobalt.—Standard solutions of cobalt nitrate were prepared by dissolution in dilute nitric acid of the metal prepared by electrodeposition from ammoniacal solutions of Merck's *pro analysi* cobalt sulphate, a potential difference of 4 v. being used. The alkalimetric titration of these solutions at room temperature was not satisfactory with colour indicators, owing to serious masking of the end-point by the presence of the dark blue precipitate. Quantitative conversion of any basic nitrates and of the dark blue α-hydroxide into the pale rose β-hydroxide was accomplished by conducting the titration hot. The results are summarised below, and certain conclusions may be drawn. For instance, it was

Theoretical titre: 25·35 ml.

Titration no.	Indicator.	pH Range.	Temp. at end-pt.	Titre, ml.	Blank, ml.	Corrected titre, ml.
1	C.R.	7·0—8·8	90°	—	—	—
2	T.B.	8·0—9·6	90	—	—	—
3	P.P.	8·0—9·8	90	25·30	0·04	25·26
4	T.P.	9·3—10·5	90	25·55	0·21	25·34
5	T.P.	9·3—10·5	25	25·35	0	25·35

evident from titrations nos. 1 and 2 that β-cobalt hydroxide exerted an intense adsorptive power for *o*-cresol-red and thymol-blue. The colour change in the supernatant liquor was indistinct, even when a relatively large amount of indicator was employed. Titration no. 3 was conducted with the aid of phenolphthalein, which showed a fairly distinct colour change despite the presence of the rose hydroxide. Nevertheless, the use of this indicator is not to be recommended since, even at a high temperature, it leads to slight under-titration. Further, in the presence of the rose hydroxide, a colour change to blue, as obtained with the aid of thymolphthalein, is better visible than one to red or violet, and titration no. 4 indicated that this end-point corresponded to quantitative formation of $Co(OH)_2$.

However, increase in temperature mars the colour changes of most indicators, including thymolphthalein: although its colour change is sufficiently vivid in the presence of white cadmium hydroxide (see above) even at high temperatures, yet the rose cobalt hydroxide tends to mask the end-point. Also, the use of thymolphthalein in hot solution requires the application of " blank " corrections. All these drawbacks may be eliminated by completing the last stage of the titration at room temperature. For instance, titration no. 5 was carried out in hot solution to within 0·2—0·3 ml. of the approximately determined end-point, the solution was cooled, indicator added, and the last few drops of alkali introduced at room temperature. A series of titrations thus conducted has shown that, unless the solution is cooled too soon, the relatively small amount of blue precipitate produced does not interfere appreciably

with the definition of the end-point. A latitude of 4—5% of the total titre is permissible when titrating 0·1N-solutions, though it is preferable to approach the end-point more closely once the approximate titration value is known. Incidentally, these results provide additional evidence that the composition of the blue precipitate produced at relatively high pH values also corresponds to $Co(OH)_4$.

Further, it proved to be immaterial whether the major part of the titration was conducted hot or cold, the only requirement being that the solution had to be heated just before the end-point. Nevertheless, it is preferable to conduct the first part of the titration at above 70°, since this results in rapid flocculation of the precipitate, and simplifies detection of slight colour changes in the supernatant liquid.

On the basis of the above considerations, the following procedure is recommended for the alkalimetric titration of cobalt solutions. (*a*) A close approximation to the true titration value is obtained by titrating the solution boiling hot, with thorough agitation near the end-point, 2 ml. of 0·05% thymolphthalein solution in 70% alcohol being used per 100 ml. of liquid present at the end-point. (*b*) Once the approximate titration value is known, the solution is titrated at 70—80° to within 0·2—0·3 ml. of the end-point, then boiled with thorough agitation until the blue precipitate has been converted into the rose one. The solution is then cooled, the indicator introduced, and the titration continued to the first appearance of blue in the supernatant liquid.

The results obtained by this procedure are shown below.

Co, g.-ions per l.	Vol. titrated, ml.	Alkali used, N.	Acid, ml.	Acid + Co, ml.	Co, ml. Found.	Co, ml. Calc.	Error, ml.
0·5001	20	1·003	4·32	24·28	19·96	19·95	+0·01
0·4998	20	1·003	8·14	28·11	19·97	19·94	+0·03
0·05110	20	0·1202	10·05	27·03	16·98	17·00	−0·02
0·05015	20	0·1202	6·24	22·93	16·69	16·69	±0
0·01010	100	0·1202	4·37	21·15	16·78	16·81	−0·03
0·01008	100	0·1202	4·15	20·90	16·75	16·77	−0·02

Anion effect. The recorded results were obtained with solutions containing nitrate as the only anion. Chloride and sulphate must be absent on account of the comparative stability of the corresponding basic salts of cobalt. Sulphate ions can be removed by addition of chloride-free barium nitrate solution in excess, and cobalt determined directly in the presence of the precipitate.

Note.—The alkalimetric determinations described in this paper have been carried out by a large number of degree students, and proved to be accurate, rapid, and expedient.

Investigations are in progress on the extension of the method to several other metals separately and in admixture.

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[*Received, July 24th*, 1950.]

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224. *An Experimental Study of Some Potentially Tautomeric 2- and 4(6)-Substituted Pyrimidines.*

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Experiments have been carried out with the object of throwing fresh light on the structure, in aqueous solutions, of pyrimidines bearing potential hydroxyl, thiol, or amino-groups in the 2- or 4(6)-positions, by the study of compounds containing not more than one such substituent. The light absorption of the potential hydroxy- and mercapto-compounds was compared with that of the corresponding (i) *O*- or *S*- and (ii) *N*-methylated derivatives at pH values carefully chosen in relation to the pK_a values of each substance to ensure the presence only of neutral molecules, cations, or, where possible, of anions. The results clearly indicate a decision in favour of the pyrimidone and thiopyrimidone structures. The situation is less clear with the potential 2- and 4(6)-aminopyrimidines. The structure of uracil is also discussed.

ANOMALOUS chemical behaviour has long been recognised in pyrimidines bearing in the 2- or 4(6)-position a potential hydroxyl, thiol, or amino-group (cf. Lythgoe, *Quart. Reviews*, 1949, **3**, 181), and similar anomalous behaviour is observable in condensed pyrimidines, such as the purines and pteridines bearing such substituents in the pyrimidine ring. In view of the biological significance of representatives of all three ring systems, considerable interest

attaches to the structure, in particular, of potential hydroxy- and amino-pyrimidines, -purines, and -pteridines in aqueous media. In each case, the potentially prototropic system

$$(A)\ \text{-NH-C:X} \rightleftarrows \text{-N:C-XH}\ (B)$$

where X = O, S, or NH, is involved, and the presence of one such group in a pyrimidine in the 1 : 2(2 : 3)- or the 3 : 4(1 : 6)-position may, or may not, influence considerably the behaviour of a second in the 3 : 4(1 : 6)-, or the 1 : 2(2 : 3)-position. In the case of 4 : 6-disubstituted pyrimidines at least one substituent must be present as a formal hydroxyl, thiol, or amino-group, as in (*B*) (cf. Baddiley, Lythgoe, and Todd, *J.*, 1943, 571). An indication of differential behaviour of potential thiol substituents in the 2- and 4-positions of the pyrimidine nucleus is found in the reaction between potential 2 : 4-dimercaptopyrimidines and ammonia (or amines), whereby *only* the potential 4-thiol group is replaced by an amino (or substituted amino)-group (Hitchings *et al.*, *J. Biol. Chem.*, 1949, **177**, 357; Russell *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 2279), and the replacement of the potential 4-thiol group may be interpreted in terms of nucleophilic attack by the ammonia, or amine, at a >C:S group, as in (*A*; X = S), the potential 2-thiol group remaining unaffected as in (*B*; X = S). By way of contrast, similar reaction of 2 : 4-diethoxy- and 2 : 4-dichloro-pyrimidines with ammonia results in the replacement of both substituents at roughly equal rates with the formation of mixtures of products (Hitchings *et al.*, *loc. cit.*; present communication), yet controlled catalytic hydrogenation of 2 : 4-dichloro-6-methylpyrimidine has been made the basis of a method for the preparation of 2-chloro-4-methyl-pyrimidine (see below). That a potential 6-hydroxy-group in purines exists as in (*A*; X = O) appears to be implicit in the electrolytic reduction of uric acid, xanthine, and theobromine to the 6-deoxy-derivatives (purone, deoxyxanthine, and deoxytheobromine) (Tafel, *Ber.*, 1899, **32**, 3194, and later papers; C. F. Boehringer ü. Söhne, D.R.-P. 108,577), while 9-methyluric acid and 7 : 9-dimethyluric acid give tetrahydro-6 : 8-diketo-2-methoxy-1 : 7 : 9-trimethylpurine but no 6-methoxylated purine with diazomethane (Biltz, *J. pr. Chem.*, 1936, **145**, 94). From a systematic study of the action of diazomethane on amides and potential amides, Arndt (*Rev. Fac. Sci. Istanbul*, 1936, **1**, 1; 1944, *A*, **9**, 19; Arndt, Loewe, and Ergener, *ibid.*, 1948, *A*, **13**, 103; Ergener, *ibid.*, 1950, *A*, **15**, 91) concludes that open-chain amides never exhibit tautomerism [(*A*) ⟶ (*B*); X = O] (cf. Biltz, *Ber.*, 1939, **72**, 807), that a potential amide group incorporated into a heterocyclic ring, as in potential 2- and 4(6)-hydroxypyrimidines, rarely shows tautomeric behaviour [(*A*) ⟶ (*B*); X = O], and that the group –CO·NH·CO–, such as may be present in uracil (see below), never exhibits tautomerism. The reservation should be made, however, that it is open to doubt to what extent results obtained in ethereal solution with diazomethane are applicable to aqueous solutions since the position of equilibrium in prototropic systems, and their mobility, depend to a considerable degree on the milieu as well as on internal factors.

The usual reactions for hydroxyl groups are difficult to carry out or fail with potential 2- or 4(6)-hydroxypyrimidines, and neither potential 2- nor 4(6)-aminopyrimidines show typical amino-group behaviour towards acylating agents and sugars (Baddiley, Lythgoe, and Todd, *loc. cit.*), although 5-aminopyrimidines are acylated normally (Isay, *Ber.*, 1906, **39**, 257; Levene and Senior, *J. Biol. Chem.*, 1916, **25**, 617). The ability of potential amino-groups in the 4(6)-position of the pyrimidine ring to undergo facile hydrolytic cleavage is indicated by the fact that alkaline permanganate degradation of aminopterin gives 2-" amino "-4-" hydroxy "-pteridine-6-carboxylic acid and not the expected 2 : 4-di-" amino "-compound (Seeger *et al.*, *J. Amer. Chem. Soc.*, 1949, **71**, 1753). Potential 4-amino-groups in pteridines may readily be hydrolysed by mineral acid although resistant to nitrous acid, and potential 2-amino-substituents are more stable to hydrolysis but react with nitrous acid (Taylor and Cain, *J. Amer. Chem. Soc.*, 1949, **71**, 2282, 2538). These observations suggest that a potential amino-group in the 4-position behaves as it might be expected to do from structure (*A*; X = NH), while a potential 2-amino-group behaves more in accordance with (*B*; X = NH), yet 2-" hydroxypyrimidine " has been prepared by alkaline hydrolysis of 2-" aminopyrimidine " (Brown, *Nature*, 1950, **165**, 1010). The above cursory, and far from complete, review of the reactions of potential hydroxy-, mercapto- and amino-pyrimidines and condensed pyrimidines conveys some impression of the difficulties in the way of attempts to assign classical structures to these substances on the basis of their reactions as the normal states of these molecules are undoubtedly profoundly disturbed by electromeric effects brought into play under the influence of reagents.

We have therefore attempted to obtain fresh light on the normal structures in aqueous solution of potential 2- or 4(6)-hydroxy- or -mercapto-pyrimidines by comparison of their ultra-violet light absorption with that of corresponding *O*-, or *S*-, and *N*-methylated derivatives;

for the potential 2- or 4(6)-aminopyrimidines however, we have not had access to the necessary range of methylated reference compounds. There have been many studies of ultra-violet light absorption of substituted pyrimidines reported previously but these, for the most part, have dealt with the more accessible pyrimidines carrying two, and often more, functional groups [*e.g.*, Austin, *J. Amer. Chem. Soc.*, 1934, **56**, 2141; Cavalieri *et al.*, *ibid.*, 1948, **70**, 3875; 1950, **72**, 2587; Elion *et al.*, *ibid.*, 1946, **68**, 2137; Heyroth and Loofbourow, *ibid.*, 1931, **53**, 3441; 1934, **56**, 1728; Loofbourow *et al.*, *ibid.*, 1943, **65**, 148; *J.*, 1940, 1275; Miller *et al.*, *J. Amer. Chem. Soc.*, 1945, **67**, 2206; Stimson, *ibid.*, 1942, **64**, 1604; Stimson *et al.*, *ibid.*, (i) 1941, **63**, 1827, (ii) 1943, **65**, 151, and (iii), 1945, **67**, 847, 2191; Stuckey, *Quart. J. Pharm.*, (i) 1940, **13**, 226, (ii) 1941, **14**, 217, and (iii), 1942, **15**, 370, 377; *J. Pharm. Pharmacol.*, 1949, **1**, 382], and there are few reports of any pyrimidines containing but one potentially prototropic system [(*A*) $\rightleftarrows$ (*B*)] having been examined (Smakula, *Z. physiol. Chem.*, 1934, **230**, 231; Williams *et al.*, *J. Amer. Chem. Soc.*, 1935, **57**, 1093; 1937, **59**, 528; Wintersteiner *et al.*, *ibid.*, 1935, **57**, 517). The value of some of the previous work carried out on aqueous solutions must really be regarded as slight since the hydrogen-ion concentrations at which ultra-violet light absorption has been measured have frequently been chosen without either knowledge of, or any reference to, the pK_a values of the substances being studied, with the result that absorption measurements have often been made on mixtures of ions and neutal molecules, and changes in the shapes of extinction curves with changes in pH have been attributed to " enolisation," whereas ionisation has really been the explanation of the effects observed.

For ease of access, all the compounds examined by the present authors had, in addition to one potentially prototropic system, a methyl group in the 6(4)-position, and, in a few cases, two methyl groups were present—in the 4- and the 6-position. It was not expected that such *C*-methyl groups would interfere to any marked degree with the observations it was intended to make, and this assumption was justified by the results obtained. 4-Methyl-2-methylthiopyrimidine (I) was obtained in good yield by dechlorination of 4-chloro-6-methyl-2-methylthiopyrimidine, and gave, on hydrolysis with hydrochloric acid, the hydrochloride of what may be either 2-hydroxy-4-methylpyrimidine (II) or 4-methyl-2-pyrimidone (III); the latter may also be represented as the 6-methyl compound (III*a*) but, for present purposes, no distinction exists between (III) and (III*a*), and further reference to such isomerism will not be made in this communication. On treatment with phosphoryl chloride (II)/(III) gave 2-chloro-4-methylpyrimidine in poor yield, and addition of phosphorus pentachloride introduced unwanted halogen (cf. Childress and McKee, *J. Amer. Chem. Soc.*, 1950, **72**, 4271). 2-Chloro-4-methylpyrimidine, however, could be obtained conveniently by controlled catalytic hydrogenation of 2 : 4-dichloro-6-methylpyrimidine, thus giving access to 2-methoxy-4-methylpyrimidine (IV) by reaction with sodium methoxide. In contrast with the experience of McOmie and Boarland (*Chem. and Ind.*, 1950, 602) who could not isolate the intermediate thiuronium salt in the reaction between 2-chloropyrimidine and thiourea, 2-chloro-4-methylpyrimidine and thiourea gave *S*-4′-methyl-2′-pyrimidylthiuronium chloride yielding on decomposition the hydrochloride of 2-mercapto-4-methylpyrimidine (V) or 4-methyl-2-thiopyrimidone (VI). 4-Hydroxy-6-methylpyrimidine (VII), or 6-methyl-4-pyrimidone (VIII), was readily obtained by desulphurisation of 6-methyl-2-thiouracil with Raney nickel, and gave 4-chloro-6-methylpyrimidine on treatment with phosphoryl chloride. By reaction with sodium methoxide and sodium methyl sulphide 4-chloro-6-methylpyrimidine readily gave 4-methoxy-6-methylpyrimidine (IX) and 6-methyl-4-methylthiopyrimidine (X) respectively, but no intermediate thiuronium salt could be isolated in the reaction with thiourea (cf. McOmie and Boarland, *loc. cit.*) and the product isolated consisted of 4-mercapto-6-methylpyrimidine (XI) or 6-methyl-4-thiopyrimidone (XII). As *N*-methylated reference compounds, 1 : 4 : 6-trimethyl-2-pyrimidone (XIII) and 1 : 4 : 6-trimethyl-2-thiopyrimidone (XIV) were obtained by condensation of acetylacetone with methylurea and methylthiourea respectively, and the methiodide (XV) of (XIII) was also prepared for comparison with the univalent cation formed by (XIII) in acid solution. Methylation of (VII)/(VIII) with diazomethane yielded *N* : 6-dimethyl-4-pyrimidone which may have either the structure (XVI) or the structure (XVII), of which, for a reason to be given later, (XVI) is preferred. Structures analogous to (XVII) may also be considered in relation to (VII)/(VIII) and (XI)/(XII) but evidence to show whether these are of importance is not available.

Ammonolysis of 2 : 4-dichloro-6-methylpyrimidine gave a mixture of products consisting of what may be called, for the sake of brevity, 2-amino-4-chloro-, 4-amino-2-chloro-, and 2 : 4-diamino-6-methylpyrimidine. Catalytic hydrogenation of the aminochloro-compounds afforded

(I.) Y = SMe
(II.) Y = OH
(IV.) Y = OMe
(V.) Y = SH
(XVIII.) Y = NH_2

(III.) Z = O
(VI.) Z = S
(XIX.) Z = NH

(IIIa.)

(XIII.) Z = O
(XIV.) Z = S

(VII.) Y = OH
(IX.) Y = OMe
(X.) Y = SMe
(XI.) Y = SH
(XX.) Y = NH_2

(VIII.) Z = O
(XII.) Z = S
(XXI.) Z = NH

(XVI.)

(XVII.)

	Compound.	pK_{a_1}.	pK_{a_2}.	Ultra-violet light absorption. pH of aqueous solution.	$\lambda_{max.}$	$\log_{10} \epsilon_{max.}$
(III)	4-Methyl-2-pyrimidone	3·15	9·8	7·0	213, 296	4·05, 3·77
				1·0	305	3·85
				13·0	220, 290	4·06, 3·76
(XIII)	1 : 4 : 6-Trimethyl-2-pyrimidone	4·0	—	7·0	218, 297	3·82, 3·82
				0·0	307	3·96
(XV)	1 : 4 : 6-Trimethyl-2-pyrimidone methiodide	—	—	0·0	223, 311	4·18, 4·06
(IV)	2-Methoxy-4-methylpyrimidine	2·1	—	7·0, 11·0	264	3·73
				0·0	272	3·85
(VI)	4-Methyl-2-thiopyrimidone	2·2	8·0	4·7	215, 277, 338	4·01, 4·28, 3·51
				0·0	221, 285, 366	3·9, 4·4, 3·15
				11·0	269	4·24
(XIV)	1 : 4 : 6-Trimethyl-2-thiopyrimidone	3·15	—	7·0	220, 277, 332	4·03, 4·24, 3·65
				0·0	225, 283, 355	3·95, 4·37, 3·41
(I)	4-Methyl-2-methylthiopyrimidine	1·95	—	7·0, 11·0	210, 250	3·6, 4·14
				0·0	215, 253, 304	3·8, 4·15, 3·66
(VIII)	6-Methyl-4-pyrimidone	2·15	9·0	4·7	228, 263 *	3·86, 3·5 *
				0·0	229	4·02
				13·0	230, 261	4·03, 3·58
(XVI)	*N* : 6-Dimethyl-4-pyrimidone	2·1	—	7·0	224, 268	3·75, 3·56
				0·0	231, 260 †	3·94, 3·45
(IX)	4-Methoxy-6-methylpyrimidine	3·65	—	7·0, 13·0	213, 247	3·67, 3·52
				1·0	244	3·93
(XII)	6-Methyl-4-thiopyrimidone	1·8	7·3	4·7	288, 322	4·0, 4·05
				0·0	312	4·25
				11·0	292	4·2
(X)	6-Methyl-4-methylthiopyrimidine	3·25	—	7·0, 11·0	213, 277	3·84, 4·01
				1·0	223, 300	3·82, 4·3
(XVIII)/ (XIX)	2-Amino-4-methylpyrimidine	4·25 ‡	—	13·0	225, 289	4·09, 3·6
				0·0	222, 299	4·13, 3·68
(XX)/ (XXI)	4-Amino-6-methylpyrimidine	6·25	—	13·0	234, 264	3·95, 3·45
				0·0	250	4·18
(XXII)	5-Amino-4-methylpyrimidine	3·15	—	13·0	234, 293	3·91, 3·55
				0·0	253, 324	4·05, 3·6
(XXIII)	4-Methylpyrimidine	2·0 ‡	—	7·0	244	3·53
				0·0	244	3·7
(XXX; R = Me)	6-Methyluracil	~1·2	9·7	4·62	261	4·00
				13·0	277	3·83
(XXIX; R = Me)	1 : 3 : 6-Trimethyluracil	—	—	7·0	268	4·00
(XXVIII; R = R′ = Me)	2-Methoxy-6-methyl-4-pyrimidone	~1·6	8·4	4·62	253	3·91
				13·0	222, 263	3·83, 3·87

* From Williams, Ruehle, and Finkelstein (*loc. cit.*). † Inflexion.
‡ Albert, Goldacre, and Phillips (*loc. cit.*) record 4·15 and 1·98 respectively.

FIG. 1. FIG. 2

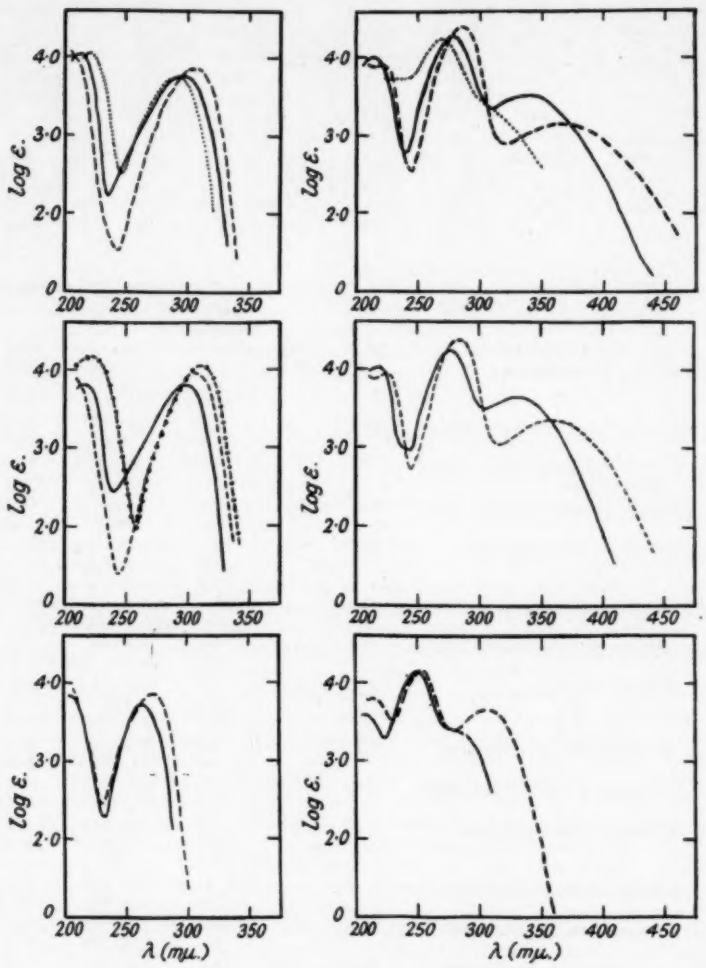


FIG. 1.

Top: 2-*Hydroxy*-4-*methylpyrimidine* (*II*) *or* 4(6)-*methyl*-2-*pyrimidone* (*III*) *in acid* (– – – –), *neutral* (———), *and alkaline* (· · · · ·) *solution.*
Centre: 1 : 4 : 6-*Trimethyl*-2-*pyrimidone* (*XIII*) *in acid* (– – – –) *and neutral* (———) *solution.* 1 : 4 : 6-*Trimethyl*-2-*pyrimidone methiodide* (*XV*) *in acid* (· — · — · — ·) *solution.*
Bottom: 2-*Methoxy*-4-*methylpyrimidine* (*IV*) *in acid* (– – – –) *and neutral* (———) *solution.*

FIG. 2.

Top: 2-*Mercapto*-4-*methylpyrimidine* (*V*) *or* 4(6)-*methyl*-2-*thiopyrimidone* (*VI*).
Centre: 1 : 4 : 6-*Trimethyl*-2-*thiopyrimidone* (XIV).
Bottom: 4-*Methyl*-2-*methylthiopyrimidine* (*I*).
In acid (– – – –), *neutral* (———), *and alkaline* (· · · · ·) *solution.*

FIG. 3.

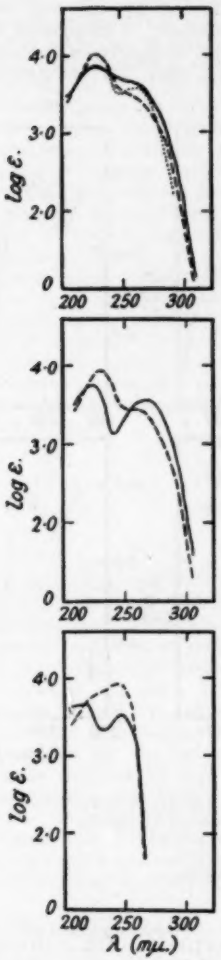


FIG. 4.

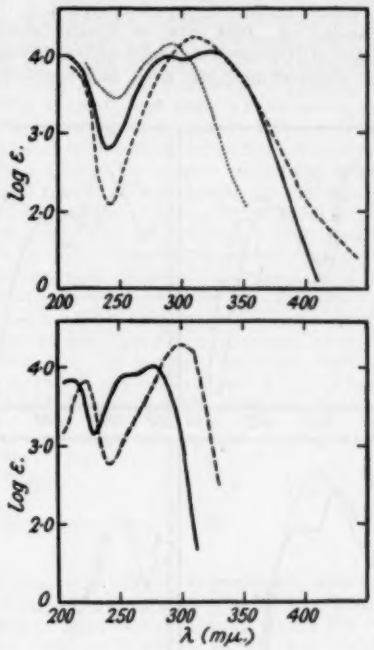


FIG. 3.

Top : 4-*Hydroxy*-6-*methylpyrimidine* (*VII*) *or* 6-*methyl*-4-*pyrimidone* (*VIII*).
Centre : *N* : 6-*Dimethyl*-4-*pyrimidone* (*XVI*)/(*XVII*).
Bottom : 4-*Methoxy*-6-*methylpyrimidine* (*IX*).
In acid (– – – –), *neutral* (———), *and alkaline* (· · · · ·) *solution.*

FIG. 4.

Top : 4-*Mercapto*-6-*methylpyrimidine* (*XI*) *or* 6-*methyl*-4-*thiopyrimidone* (*XII*).
Bottom : 6-*Methyl*-4-*methylthiopyrimidine* (*X*).
In acid (– – – –), *neutral* (———), *and alkaline* (· · · · ·) *solution.*

what may briefly be termed 2-amino-4-methyl- (XVIII)/(XIX) and 4-amino-6-methylpyrimidine (XX)/(XXI), without, however, implying any preference whatever for structures (XVIII) and (XX). 5-Amino-4-methylpyrimidine (XXII) was obtained by reduction, in two stages, of 2 : 4-dichloro-6-methyl-5-nitropyrimidine, obtained by applying Baddiley and Topham's technique (*J.*, 1944, 678) to 6-methyl-5-nitrouracil; a by-product in the latter reaction consisted of 2(4)-chloro-6-methyl-4(2)-methylanilino-5-nitropyrimidine analogous with the by-product obtained by King, King, and Spensley (*J.*, 1947, 1247) in applying the same

FIG. 5. FIG. 6.

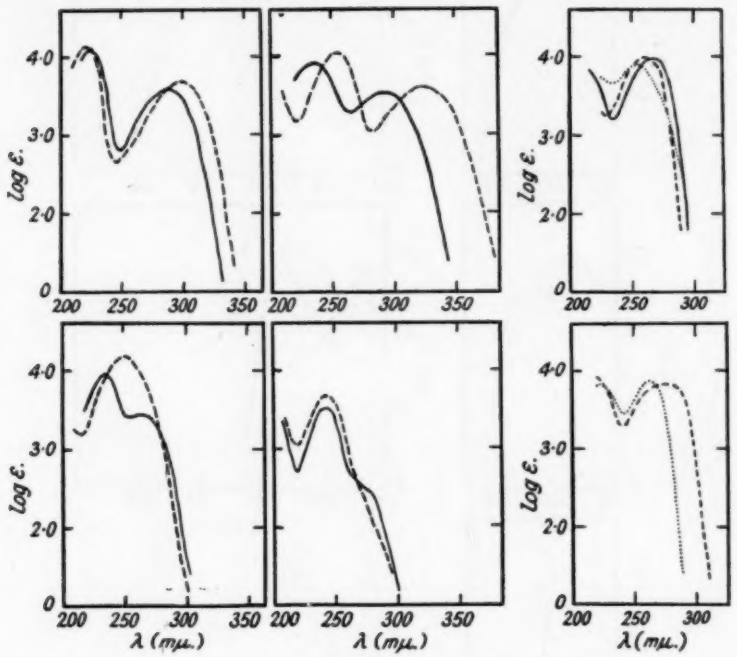


FIG. 5.

Top (left) : 2-Amino-4-methylpyrimidine (XVIII)/(XIX).
Bottom (left) : 4-Amino-6-methylpyrimidine (XX)/(XXI).
Top (right) : 5-Amino-4-methylpyrimidine (XXII).
Bottom (right) : 4-Methylpyrimidine (XXIII).
In acid (– – – –) and neutral (———) solution.

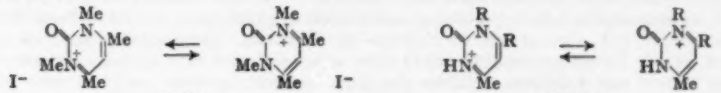
FIG. 6.

Top : 6-Methyluracil (XXX; R = Me) *at pH* 4·62 (– – – –); 1 : 3 : 6-*trimethyluracil* (*XXIX*; R = Me) *at pH* 7·0 (———); 2-*methoxy-6-methyl-4-pyrimidone* (XXVIII; R = Me) *at pH* 4·62 (· · · · · ·).
Bottom : 6-Methyluracil at pH 13 (– – – –); 2-*methoxy-6-methyl-4-pyrimidone* (· · · · · ·) *at pH* 13.

technique to barbituric acid. 4-Methylpyrimidine (XXIII) was prepared by dehalogenation of 2 : 4-dichloro-6-methylpyrimidine.

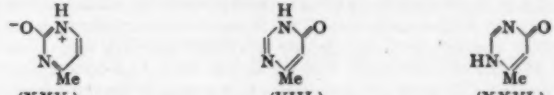
The pK_a values of all the substances being examined for ultra-violet light absorption were first determined by potentiometric titration and are recorded in the table. The light absorption was thereafter measured in aqueous solution at pH values chosen in relation to the pK_a values in such a way that essentially only neutral molecules, univalent cations, or where possible, univalent anions could have been present. Thus, measurements in acid solution, except for the limiting cases of the two most feebly basic compounds, (I) and (XI)/(XII), were carried out at pH values numerically at least 2 below the basic pK_a values, and in alkaline solution, in the case of acidic substances, at pH values numerically at least 2 above the acidic pK_a

value, ensuring at both extremes the presence of over 99% of the solute in the ionised condition. The light absorption of the un-ionised compounds was similarly measured in the middle of the pH range at pH values differing by at least 2 numerically from the relevant pK_a values, a pH value of less than 7 only being necessary in the cases of the more acidic substances. The wavelengths of maximum extinction, and the logarithms of the molecular extinction coefficients, are recorded in the table but, as these do not convey an adequate impression of the absorption characteristics, light-extinction curves are shown in Figs. 1—6. Comparison of the light-extinction curves for (II)/(III) with those of 1 : 4 : 6-trimethyl-2-pyrimidone (XIII) and 2-methoxy-4-methylpyrimidine (IV) (Fig. 1) shows that there is close correspondence between the neutral and cationic species of the first two, but considerable difference between these and (IV), thus indicating a decision in favour of the 4-methyl-2-pyrimidone structure (III) for the potential 2-hydroxy-4-methylpyrimidine (II). The greater similarity between the light absorption of (XIII) in acid solution and that of its methiodide (XV), compared with that of (IV) in acid solution, indicates that in the formation of cations from (XIII) and (III) the proton is accepted by the second ring-nitrogen atom with the production of an extended resonating amidinium system (XXIV; R = Me or H). These observations also contraindicate the substantial contribution of the dipolar ionic form (XXV) to the structure of (III) (cf. Arndt, *loc. cit.*). Similar comparison of the light-extinction curves for (V)/(VI) with those for 1 : 4 : 6-trimethyl-2-thiopyrimidone (XIV) and 4-methyl-2-methylthiopyrimidine (I) (Fig. 2) likewise clearly indicates a decision in favour of the 4-methyl-2-thiopyrimidone structure (VI) for the potential 2-mercapto-4-methylpyrimidine (V). It is clear, moreover, that the addition of *C*-methyl groups in passing from (III) to (XIII) and from (VI) to (XIV) has had practically no effect on the absorption characteristics (cf. Williams, Ruehle, and Finkelstein, *J. Amer. Chem. Soc.*, 1935, **57**, 1093).



(XV.) (XXIV.)

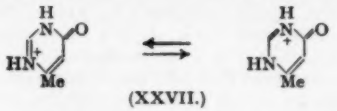
The light absorption of (VII)/(VIII) in acid solution is practically identical with that of *N* : 6-dimethyl-4-pyrimidone (XVI)/(XVII) in acid solution (Fig. 3). In neutral solution, the greater resolution achieved in the case of the latter compound makes the resemblance less striking, although it should be pointed out that Williams, Ruehle, and Finkelstein (*loc. cit.*) succeeded in obtaining rather better resolution of the longer-wave maximum of (VII)/(VIII) in neutral solution. In both acid and neutral solution, the light absorption of these two compounds, (VII)/(VIII) and (XVI)/(XVII), differs considerably from that of 4-methoxy-6-methylpyrimidine (IX), leading to the conclusion that the 6-methyl-4-pyrimidone structure (VIII) is preferred for the potential 4-hydroxy-6-methylpyrimidine (VII). The problem is rather more complex in this case than with the 2-pyrimidone since two types of structure are possible, *viz.*, (VIII) and (XXVI), in analogy with *N* : 6-dimethyl-4-pyrimidone (XVI)/(XVII). Structures (VIII) and (XVI) respectively are preferred because of the fact that no bathochromic shift is observed in passing from the one substance to the other on the analogy with the pyridones and *N*-methylpyridones, where *N*-methylation in 4-pyridone, which is analogous with (XXVI), is accompanied by a small bathochromic shift, while no such shift is



(XXV.) (VIII.) (XXVI.)

observed in passing from 2-pyridone to *N*-methyl-2-pyridone (Specker and Gawrosch, *Ber.*, 1942, **75**, 1338) or in passing from 2-quinolone to *N*-methyl-2-quinolone (Morton and Rogers, *J.*, 1925, **127**, 2698); further instances of this empirical rule will be noted later in connection with the structure of uracil. The light absorptions of 2-pyridone, *N*-methyl-2-pyridone, and 2-ethoxypyridine in acid solution resemble each other closely, as do those of 4-pyridone, *N*-methyl-4-pyridone, and 4-methoxypyridine in acid solution (Specker and Gawrosch, *loc. cit.*; cf. Ewing and Steck, *J. Amer. Chem. Soc.*, 1946, **68**, 2181, for analogous observations on 4-quinolone and 4-methoxyquinoline), and in these cases there can be no doubt that the proton

is accepted by the oxygen atoms of the pyridones in cation formation. On the other hand, no such behaviour is shown in the light absorptions of 6-methyl-4-pyrimidone (VII) and 4-methoxy-6-methylpyrimidine (IX) in acid solution, and, as already noted in the case of the 2-pyrimidone (III), cation formation by 6-methyl-4-pyrimidone (VIII) must take place by the acceptance of the proton by the nitrogen atom not already carrying a hydrogen atom, with the formation of an



(XXVII.)

amidinium system (XXVII). Although no comparison with the appropriate *N*-methylated reference compound has been made, the 6-methyl-4-thiopyrimidone structure (XII) is favoured for the potential 4-mercapto-6-methylpyrimidine (XI), because its absorption differs considerably from that of 6-methyl-4-methylthiopyrimidine (X) (Fig. 4).

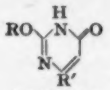
A number of significant regularities are apparent in the pK_a values of the pyrimidones, thiopyrimidones, methoxypyrimidines, and methylthiopyrimidines. Thus the sulphur-containing compounds are invariably less basic and, where possible, more acidic than their oxygen analogues. 4-Methoxy-6-methyl- (IX) and 6-methyl-4-methylthio-pyrimidine (X) are stronger bases than 2-methoxy-4-methyl- (IV) and 4-methyl-2-methylthio-pyrimidine (I), while the situation is reversed in the pyrimidones, 4-methyl-2-pyrimidone (III) and 4-methyl-2-thio-pyrimidone (VI) being stronger bases than 6-methyl-4-pyrimidone (VIII) and 6-methyl-4-thiopyrimidone (XII) respectively.

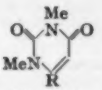
With the potential aminopyrimidines, the light-absorption measurements (Fig. 5), in the absence of comparable data for reference compounds in which prototropy has been blocked by methylation, do not allow of final conclusions being reached. On general grounds, it might be expected that a 5-aminopyrimidine would show some analogies with aromatic primary amines such as aniline and toluidine. Unlike the latter amines, however, which absorb at longer wave-lengths than their parent hydrocarbons and assume the absorption characteristics of the latter in acid solution, the absorption of 5-amino-4-methylpyrimidine (XXII) in acid solution is quite unlike that of 4-methylpyrimidine (XXIII) in neutral solution, indicating that the proton is accepted by one of the ring-nitrogen atoms of (XXII) in cation formation, as with the aminoacridines (Albert and Goldacre, *J.*, 1943 454) and the aminopyridines (Steck and Ewing, *J. Amer. Chem. Soc.*, 1948, **70**, 3397). 4-Amino-6-methylpyrimidine (XX)/(XXI) is a substantially stronger base than 2-amino-4-methylpyrimidine (XVIII)/(XIX), just as 4-amino-pyridine, -quinoline, and -quinazoline are stronger bases than 2-amino-pyridine, -quinoline, and -quinazoline (cf. Albert, Goldacre, and Phillips, *J.*, 1948, 2240).

In the light of the conclusions reached above that the potential 2- and 4(6)-hydroxy- and -mercapto-pyrimidines, which we have examined, are to be represented as pyrimidones and thiopyrimidones respectively, a re-examination of the structure of uracil seemed to be warranted. Austin (*J. Amer. Chem. Soc.*, 1934, **56**, 2141) inferred that uracil had structure (XXVIII; R = R′ = H) from the fact that its light absorption in alcohol resembled that of 3-methyluracil, while differing from those of 1-methyluracil, 1 : 3-dimethyluracil (XXIX; R = H), 2 : 4-diethoxypyrimidine, and 4-ethoxy-1-methyl-2-pyrimidone, but no comparison with a reference compound of the type (XXVIII; R = alkyl, R′ = H) was attempted. Inspection of Austin's light-extinction curves shows that those of uracil and 3-methyluracil are indeed alike, while those of 1-methyluracil * and 1 : 3-dimethyluracil both show, in comparison, a small bathochromic shift, similar to that commented upon already in connection with 4-pyridone and 1-methyl-4-pyridone. Like the latter substance, 1-methyluracil and 1 : 3-dimethyluracil both have a *N*-methyl group and a >C:O group, or potential >C:O group, in the same relative 1 : 4-positions, indicating the doubtful relevance of the small bathochromic shifts observed. On these grounds we felt disinclined to agree with the rejection of structure (XXX; R = H) for uracil, and have extended Austin's study by comparing the light absorption of 2-methoxy-6-methyl-4-pyrimidone (XXVIII; R = R′ = Me), a reference compound of the type previously omitted, with those of 6-methyluracil and 1 : 3 : 6-trimethyluracil (XXIX; R = Me) in aqueous solution (Fig. 6). It is obvious that the light absorption of (XXVIII; R = R′ = Me) is unlike that of 6-methyluracil, and that those of 6-methyluracil and 1 : 3 : 6-trimethyluracil are alike apart from the small bathochromic shift in the light absorption of the latter, which we regard as

* In addition, 1-methyluracil also appears from Austin's work to show slightly stronger absorption.

irrelevant from the structural point of view in the light of our empirical generalisation and a natural consequence of *N*-methylation on the 1-nitrogen atom relative to the >C:O group in the 4-position. From these observations it is concluded that 6-methyluracil is to be represented as (XXX; R = Me) and uracil as (XXX; R = H), in agreement with the structure assigned to uracil on the basis of methylation with diazomethane (Case and Hill, *J. Amer. Chem. Soc.*, 1930, **52**, 1536). It may also be noted in passing that an analogous structure (XXXI) is preferred for 2-thiouracil on the basis of dipole-moment measurements in dioxan solution (Schneider and Halverstadt, *J. Amer. Chem. Soc.*, 1948, **70**, 2626).


(XXVIII.)


(XXIX.)

(XXX.)

(XXXI.)

Apart from the more labile chloropyrimidines the majority of the compounds described above were kindly tested by Dr. P. D'Arcy Hart for activity against the tubercle bacillus (bovine type) in Dubos medium with albumin and Tween 80. The two thiopyrimidones, (VI) and (XII), were active at 1 in 160,000; 6-methyldithiouracil was active at 1 in 40,000, and two other compounds, (I) and (XV), were active at 1 in 6,000 and at 1 in 10,000 respectively; otherwise none was active at 1 in 6000. It may be noted that 2-thiouracil has been shown to be active *in vitro* against the tubercle bacillus (Duca and Steinbach, *Amer. Rev. Tuberc.*, 1946, **53**, 594), while negligible activity has been reported by Brooks *et al.* (*J.*, 1950, 452) for a range of alkylthiopyrimidines. Dr. R. Pitt-Rivers kindly examined the effects of (VI) and (XII) on the formation of acetylthyroxine from acetyldi-iodotyrosine *in vitro* and found 0·1 molecular equivalent to produce 74% and 55% inhibition respectively in her standardised procedure (*Biochim. Biophys. Acta*, 1948, **2**, 311).

Experimental.

4-Methyl-2-methylthiopyrimidine (I).—4-Chloro-6-methyl-2-methylthiopyrimidine (100 g.) (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 435) was added to a suspension of zinc powder (200 g.) in water (3 l.). The mixture was vigorously refluxed for 2 hours while aqueous ammonia (40 c.c.; *d* 0·880) was added in small portions from time to time; there was a slight evolution of methanethiol. After cooling, the unused zinc was removed and washed with ether. The aqueous solution was extracted several times with ether and, on fractionation of the dried extracts, *4-methyl-2-methylthiopyrimidine* distilled at 111°/15 mm. as a colourless liquid (71 g., 89%), n_D^{17} 1·5726 (Found: C, 51·7; H, 5·8. $C_6H_8N_2S$ requires C, 51·4; H, 5·7%). The *picrate* crystallised from about 5 parts of alcohol in yellow rhombohedral prisms, m. p. 106—108° (Found: C, 39·4; H, 2·8. $C_6H_8N_2S,C_6H_3O_7N_3$ requires C, 39·0; H, 3·0%).

An attempt (cf. Sprague *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 3030) to prepare the above substance from the sodium salt of hydroxymethyleneacetone and *S*-methylthiuronium sulphate in cold aqueous solution gave less than 10% of the desired material, b. p. 114—118°/22 mm., n_D^{19} 1·5723.

4-Methyl-2-pyrimidone (III) *Hydrochloride.*—4-Methyl-2-methylthiopyrimidine (71·2 g.) was refluxed with concentrated hydrochloric acid (600 c.c.) until evolution of methanethiol ceased (*ca.* 80 minutes). The reddish-brown solution was evaporated to dryness under reduced pressure, and the residue, recrystallised from a mixture of alcohol and 3N-hydrochloric acid, gave almost colourless needles (64 g., 87%) of *4-methyl-2-pyrimidone hydrochloride*, m. p. 246° (decomp.) with discoloration above 210° (Found, on material dried over phosphoric oxide for 48 hours: C, 41·3; H, 4·9; N, 19·4. $C_5H_6ON_2,HCl$ requires C, 41·0; H, 4·8; N, 19·1%).

1 : 4 : 6-Trimethyl-2-pyrimidone (XIII).—This was prepared from methylurea and acetylacetone as described by Hale (*J. Amer. Chem. Soc.*, 1914, **36**, 104). Repeated extractions with chloroform were necessary to extract the product from aqueous solution; it had m. p. 62° after recrystallisation from benzene (alumina); Hale (*loc. cit.*) records m. p. 63°. Specimens exposed to the air gradually became pink, then red, especially when impure.

1 : 4 : 6-Trimethyl-2-pyrimidone Methiodide (XV).—1 : 4 : 6-Trimethyl-2-pyrimidone (1 g.) was treated with methyl iodide (5 c.c.). The pyrimidone soon dissolved and the methiodide crystallised. After 24 hours, the excess of methyl iodide was removed and the product separated from methanol–ethyl acetate, giving pale yellow flattened needles of the *methiodide* (1·1 g.), m. p. 194° to a red liquid, after 24 hours' desiccation (Found: C, 32·2, 32·6; H, 4·8, 5·1; N, 9·8; OMe, 0. $C_8H_{13}ON_2I,H_2O$ requires C, 32·3; H, 5·1; N, 9·4%). The mother-liquors developed a deep wine-red colour when kept.

2-Chloro-4-methylpyrimidine.—(*A*) A mixture of finely powdered 2-hydroxy-4-methylpyrimidine hydrochloride (29·3 g.) and phosphoryl chloride (150 c.c.) was kept at 120—125° (oil-bath) for 1·25 hours with intermittent shaking. The evolution of hydrogen chloride, initially brisk, became slight towards the end. The cooled red solution was filtered to remove unchanged starting material (21·3 g.). The phosphoryl chloride was removed under reduced pressure at 50°, and the residue treated with ice and neutralised with sodium hydroxide. The product (4·8 g.), recovered in ether and fractionated, afforded *2-chloro-4-methylpyrimidine* (3·9 g.), b. p. 93—93·5°/17 mm., m. p. 48—50°. Recrystallisation from

light petroleum gave elongated plates with unchanged m. p. (Found: C, 46·3; H, 4·1. $C_6H_5N_2Cl$ requires C, 46·9; H, 3·9%).

Despite numerous modifications in technique no appreciably greater conversion was achieved using phosphoryl chloride, and the addition of phosphorus pentachloride led to the formation of a polychloro-derivative. A mixture of 4-methyl-2-pyrimidone hydrochloride (15·2 g.) and phosphorus pentachloride (30 g.) in phosphoryl chloride (50 g.) was refluxed for 1·5—2 hours. The phosphoryl chloride was removed in the usual way and the residue was treated with crushed ice and aqueous sodium hydroxide to pH 9. Ether was added and the crude product (13 g.) was recovered after rejection of an insoluble brown solid (3—4 g.). On fractionation there were obtained: (i) a mixture (3·44 g.), b. p. 70—132·5°/13 mm., which did not solidify on cooling, and (ii) the main bulk (6·3 g.) of the product, b. p. 132·5—134°/13 mm., which rapidly solidified when scratched; crystallisation from light petroleum afforded brilliant long prisms of 2 : x : x : x-*tetrachloro-4-methylpyrimidine*, m. p. 43·5—45° (Found: C, 26·1; H, 0·9; N, 12·2; Cl, 60·5. $C_5H_3N_2Cl_4$ requires C, 25·9; H, 0·9; N, 12·1; Cl, 60·7%).

(*B*) By use essentially of the method of Gabriel and Colman (*Ber.*, 1899, **32**, 1533), 6-methyluracil (*Org. Synth.*, **17**, 63) was converted into 2 : 4-dichloro-6-methylpyrimidine. The reaction mixture was poured into iced water and the product was recovered in ether, the extract being washed with water and thoroughly dried before fractionation. The product, obtained in 90—95% yield as compared with the 77% yield hitherto recorded, had b. p. 108°/18·5 mm.; it gradually decomposed.

A mixture of 2 : 4-dichloro-6-methylpyrimidine (81·5 g., 0·5 mole), light magnesium oxide (25 g., 25% excess), ether (100 c.c.), and water (100 c.c.) was shaken for 16 hours at room temperature with 1·2% palladised strontium carbonate (8 g.) in hydrogen under a pressure of *ca.* 3 atms.; the theoretical volume of hydrogen (11·2 l. at N.T.P.) was absorbed. The reaction mixture was filtered, the solid being well washed with ether and water, and the crude product (52 g.) was recovered in ether after bringing the pH of the aqueous phase to 10—11. On fractionation there were obtained: (i) a small fraction, b. p. up to 90°/17·5 mm., which was not further examined; (ii) a pink-coloured main fraction (35·6 g.), b. p. 94—99°/17·5 mm., which solidified on cooling; and (iii) a mixture (7·8 g.), b. p. 99—105°/17·5 mm., which did not crystallise. The main fraction (ii) was decolorised in hot light petroleum with activated alumina and, on concentration and cooling, large prisms separated, m. p. 48—50° alone and on admixture with the product obtained as in (*A*) above.

The substance liquefied when mixed at room temperature with either 2 : 4-dichloro-6-methyl- or 4-chloro-6-methyl-pyrimidine. The use of alcoholic alkali was precluded in the above hydrogenation since 2 : 4-dichloro-6-methylpyrimidine reacted exothermally in the cold with potassium hydroxide in 80% methanol to give 2 : 4-dimethoxy-6-methylpyrimidine, m. p. 65° (lit., m. p. 69—70°). Some hydrolysis also took place in the presence of aqueous alkali.

2-*Methoxy*-4-*methylpyrimidine* (IV).—2-Chloro-4-methylpyrimidine (6·4 g.) was added to a solution of sodium methoxide (from 2·8 g. of sodium) in methanol (50 c.c.). Sodium chloride was rapidly precipitated in an exothermic reaction. After 15 minutes on the water-bath, the solution was poured into water and extracted with ether. Fractionation of the extract afforded 2-*methoxy*-4-*methylpyrimidine* (5 g.) as a colourless liquid, b. p. 89°/21 mm., n_D^{21} 1·5013 (Found: C, 58·3; H, 6·5. $C_6H_8ON_2$ requires C, 58·1; H, 6·5%).

S-4-*Methyl*-2-*pyrimidylthiuronium Chloride*.—A solution of 2-chloro-4-methylpyrimidine (1·28 g.) and thiourea (0·76 g.) in ethanol (11 c.c.) was refluxed until a test drop no longer gave a dark precipitate with ammoniacal silver nitrate (*ca.* 40 minutes). Pale orange needles (1·15 g.) separated on cooling and a further quantity (0·23 g.) was obtained on concentration of the mother-liquors. The crude product was dissolved in ethanol (10 c.c.) containing a few drops of concentrated hydrochloric acid and freed from a small residue (90 mg.) of 4-methyl-2-thiopyrimidone. On cooling, S-4′-*methyl*-2′-*pyrimidylthiuronium chloride* separated in yellow needles which became pink at 160°, reddened at 180—185°, and decomposed at 185—200° (Found: C, 35·5; H, 4·3; N, 26·8. $C_6H_9N_4SCl$ requires C, 35·2; H, 4·4; N, 27·4%).

4-*Methyl*-2-*thiopyrimidone* (VI) *Hydrochloride*.—A solution of the preceding thiuronium chloride (0·88 g.) in alcohol (25 c.c.) was heated on the water-bath with a few drops of concentrated hydrochloric acid for 8 hours, the product separating slowly during that period. Recrystallisation of the product (0·5 g.) from a large volume of alcohol (300 c.c.) containing about 1·5% of concentrated hydrochloric acid by volume and concentration to small bulk (40 c.c.) gave small yellow plates of 4-*methyl*-2-*thiopyrimidone hydrochloride*, m. p. 265° (decomp.) (Found: C, 36·6; H, 4·2; N, 17·5. $C_5H_6N_2S,HCl$ requires C, 36·9; H, 4·3; N, 17·2%).

1 : 4 : 6-*Trimethyl*-2-*thiopyrimidone* (XIV).—This compound was prepared according to Hale and Williams's method (*J. Amer. Chem. Soc.*, 1915, **37**, 598) from acetylacetone and methylthiourea.

6-*Methyl*-4-*pyrimidone* (VIII).—6-Methyl-2-thiouracil (56·8 g.) (Wheeler and McFarland, *Amer. Chem. J.*, 1909, **42**, 105) was suspended in water (800 c.c.) and refluxed for 2 hours with Raney nickel (76 c.c. of sludge), which had not been exposed to temperatures exceeding 50° during its preparation. The catalyst was collected and washed with water, and the aqueous solution and washings were taken to dryness. The crude product (45 g.) was extracted with boiling ethyl acetate, leaving a sticky residue. The ethyl acetate was removed and the product was again taken up in boiling ethyl acetate with rejection of a further slight sticky residue. The extraction process was repeated twice more with the substitution of benzene for ethyl acetate, affording material (28 g., 64%) suitable for further use. Recrystallisation from ethanol (4 parts) and then from benzene (20 parts) gave pure 6-methyl-4-pyrimidone as colourless elongated prisms, m. p. 150°. Gabriel and Colman (*Ber.*, 1899, **32**, 2931) record m. p. 149—150° and Williams *et al.* (*J. Amer. Chem. Soc.*, 1937, **59**, 528), m. p. 148—149°.

N : 6-*Dimethyl*-4-*pyrimidone* (XVI).—6-Methyl-4-pyrimidone (1·5 g.) in chloroform (10 c.c.) was added to ethereal diazomethane (from 10 g. of nitrosomethylurea). The precipitate which separated immediately redissolved with evolution of heat and nitrogen. After 24 hours, the solvent and excess of

diazomethane were removed, finally at 60—70°. 4-Methoxy-6-methylpyrimidine (0·23 g.) was removed from the residue at 100°/15 mm. The solid residue was recrystallised from carbon tetrachloride (alumina), giving hard colourless prisms of N : 6-*dimethyl-4-pyrimidone* (0·8 g.), m. p. 80—82° (Found : C, 57·9; H, 6·3; N, 22·5. $C_6H_8ON_2$ requires C, 58·1; H, 6·5; N, 22·6%).

The 4-methoxy-6-methylpyrimidine, n_D^{20} 1·4949, was converted into the *picrate* with cold aqueous picric acid. It separated from water in beautiful flattened prisms, m. p. 117°, alone and on admixture with a specimen of picrate prepared from 4-methoxy-6-methylpyrimidine obtained by the previously described route (above) (Found : N, 19·8. $C_6H_8ON_2,C_6H_3O_7N_3$ requires N, 19·8%).

4-Chloro-6-methylpyrimidine.—(*A*) 6-Methyl-4-pyrimidone (18 g.) was treated with phosphoryl chloride (150 g.) essentially as described by Gabriel and Colman (*Ber.*, 1899, **32**, 2921). The mixture was heated on the boiling water-bath for 1·25 hours, dissolution being complete in ½—1 hour. The phosphoryl chloride was removed and the residue was treated with crushed ice, the product being isolated by basification and extraction with ether. On fractionation, the crude product (20 g.) gave pure 4-chloro-6-methylpyrimidine (14·8 g., 70%), b. p. 65·5—66·5°/12 mm., m. p. 34·5—36°. Gabriel and Colman (*loc. cit.*) record m. p. 38—39·5°.

(*B*) A slightly better yield was obtained by direct treatment with phosphoryl chloride of the crude desulphurisation product from 6-methyl-2-thiouracil, the overall yield from the latter being 53%.

The compound decomposed slowly, becoming orange. It could readily be purified by distillation preferably after being partitioned between ether and water, the orange colour passing into the aqueous phase.

4-Methoxy-6-methylpyrimidine (IX).—4-Chloro-6-methylpyrimidine (8·7 g.) was added to sodium methoxide (from 2·8 g. of sodium) in methanol (50 c.c.). Sodium chloride was immediately precipitated with evolution of heat. After 15 minutes on the water-bath the mixture was poured into water and the product recovered in ether. Fractionation of the extract afforded *4-methoxy-6-methylpyrimidine* as a colourless liquid (6·65 g., 79%), b. p. 69°/21 mm., n_D^{21} 1·4950 (Found : C, 58·4; H, 6·6. $C_6H_8ON_2$ requires C, 58·1; H, 6·5%).

6-Methyl-4-thiopyrimidone (XII).—A solution of 4-chloro-6-methylpyrimidine (2·57 g.) and thiourea (1·52 g.) in ethanol (25 c.c.) was refluxed for an hour. On cooling, 6-methyl-4-thiopyrimidone (1·2 g.) separated instead of the expected *S*-6′-methyl-4′-pyrimidylthiuronium chloride. The substance crystallised from acetic acid, or from a large volume of water (charcoal), in pale yellow prisms, m. p. 255—260° (decomp.) with darkening from about 190°. Gabriel and Colman (*Ber.*, 1899, **32**, 2932) record m. p. 255° (decomp.) with sintering at 190°.

A crystalline thiuronium salt could not be isolated from the reaction mixture. In another experiment the reaction was carried out in 0·2N-hydrochloric acid and again only the thiopyrimidone was isolated though in lower yield.

6-Methyl-4-methylthiopyrimidine (X).—To a solution of sodium methyl sulphide, obtained by adding 25% aqueous sodium hydroxide (25 c.c.) to *S*-methylthiuronium sulphate (18·9 g.) and collecting the evolved methanethiol in 30% aqueous sodium hydroxide (10 c.c.), there was added 4-chloro-6-methylpyrimidine (6·43 g.). The inhomogeneous mixture was kept for 4 hours at 60—80° with intermittent shaking. Alcohol (25 c.c.) was added to effect mixing, and heating was continued under reflux on the boiling water-bath for 3 hours. After removal of the alcohol by distillation, the crude product (6·5 g.) was recovered in ether. *6-Methyl-4-methylthiopyrimidine* distilled as a colourless liquid at 104°/17 mm., n_D^{20} 1·5740 (Found : C, 51·6; H, 6·1. $C_6H_8N_2S$ requires C, 51·4; H, 5·7%). The compound later solidified and recrystallisation from light petroleum gave colourless prisms, m. p. 25—28°.

Ammonolysis of 2 : 4-*Dichloro-6-methylpyrimidine.*—The proportions of the products formed in the ammonolysis of 2 : 4-dichloro-6-methylpyrimidine varied considerably according to the conditions of reaction (cf. Gabriel and Colman, *Ber.*, 1899, **32**, 2921; 1901, **34**, 1234). The general method used was as follows : 2 : 4-Dichloro-6-methylpyrimidine (80 g.) and alcoholic ammonia (500 c.c.), saturated at 0°, were heated in a stainless steel autoclave. The clean reaction mixture was taken to dryness and the residue was washed with chilled 2N-aqueous ammonia (300—400 c.c.). The dried mixture was boiled with benzene (30—40 c.c. per g.), and the hot solution was filtered and evaporated to give 2-" amino "-4-chloro-6-methylpyrimidine (A). The residue was continuously extracted with boiling benzene which slowly removed 4-" amino "-2-chloro-6-methylpyrimidine (B), leaving a " hydrochloride " (C) of 2 : 4-" diamino "-6-methylpyrimidine; alternatively, the last could be removed by crystallisation from water leaving 4-" amino "-2-chloro-6-methylpyrimidine. Three typical experiments are summarised in the following table.

Solvent.	Time of heating.	Temperature.	Yields (g.). (A).	(B).	(C).
Ethanol	5 hours	92°	28·1	32·9	nil
Ethanol	6 hours	95—105	15·6	16·5	30
Methanol	6 hours	95—105	0·8	4·5	50

2-Amino-4-chloro-6-methylpyrimidine separated from 12 parts of alcohol in colourless needles, m. p. 183°; Gabriel and Colman (*locc. cit.*) record m. p. 181—182°. 4-Amino-2-chloro-6-methylpyrimidine crystallised from 12 parts of alcohol in colourless prisms, m. p. 219·5°; Gabriel and Colman (*locc. cit.*) record m. p. 215—216°.

The " hydrochloride " (C) of 2 : 4-diamino-6-methylpyrimidine separated from ethanol (15 parts) in large tabular prisms, m. p. 213—215°. Consistent analytical figures were not obtained but they indicated approx. three molecules of base per molecule of hydrogen chloride (Found, on material dried over phosphoric oxide *in vacuo* : C, 43·8; H, 6·0; N, 41·2. $3C_4H_8N_4,HCl$ requires C, 44·1; H, 6·1; N, 41·1%). Free 2 : 4-diamino-6-methylpyrimidine, precipitated from the " hydrochloride " with 50%

aqueous potassium hydroxide solution, crystallised from water (1 c.c./g.), and then sublimed in a vacuum, had m. p. 185—186° (Found: C, 49·1; H, 6·5; N, 45·4. Calc. for $C_5H_8N_4$: C, 48·4; H, 6·5; N, 45·2%). Gabriel and Colman (*locc. cit.*) record m. p. 183—185°.

2-Amino-4-methylpyrimidine (XVIII)/(XIX).—A mixture of 2-amino-4-chloro-6-methylpyrimidine (7·2 g.) in acetone (200 c.c.) and potassium hydroxide (2·8 g.) in water (100 c.c.) was shaken with 1·2% palladised strontium carbonate (2 g.) in hydrogen at atmospheric pressure, the calculated volume of hydrogen being absorbed in 3 hours. The filtered solution was taken to dryness and the residue was extracted with boiling ethanol (70 c.c.). Evaporation of the alcohol and crystallisation of the residue from water afforded colourless plates (3·7 g.) of 2-amino-4-methylpyrimidine, m. p. 158—160°. Backer and Grevenstuk (*Rec. Trav. chim.*, 1942, **61**, 291) record m. p. 154·5—156·5°, and Gabriel and Colman (*locc. cit.*), m. p. 159—160°. The compound gradually evolved ammonia when boiled with 20% sodium hydroxide solution.

4-Amino-6-methylpyrimidine (XX)/(XXI).—A solution of 4-amino-2-chloro-6-methylpyrimidine (2·9 g.) in methanol (200 c.c.) was shaken with 5% palladised charcoal (0·4 g.) in hydrogen at atmospheric pressure. Hydrogen (470—500 c.c.) was absorbed during 16 hours and there was no subsequent absorption. The filtered solution was evaporated and the residue, in water (10 c.c.), was basified with potassium hydroxide (4 g.), which precipitated the free base (2·3 g.), m. p. 196—198°. Recrystallisation from water (6 c.c.) and vacuum-sublimation gave pure 4-amino-6-methylpyrimidine (1·42 g., 65%), m. p. 197°. Backer and Grevenstuk (*loc. cit.*) record m. p. 197—197·5°, and Gabriel and Colman (*locc. cit.*) m. p. 194—195°. The solubility in cold water was about 10%. When the compound was heated with 25% aqueous sulphuric acid to 180° for 2 hours, no darkening occurred and some 6-methyl-4-pyrimidone was isolated from the reaction mixture besides unchanged amine.

2 : 6-*Dichloro-6-methyl-5-nitropyrimidine.*—Dimethylaniline (10 g.) was added carefully to a suspension of 6-methyl-5-nitrouracil (8 g.) (Gabriel and Colman, *Ber.*, 1901, **34**, 1242) in phosphoryl chloride (40 c.c.), and the mixture was refluxed for 45 minutes. The dark green mixture was cooled, then poured on ice, and the product (8 g.) was recovered in ether. On fractional distillation there were obtained: (i) 2 : 4-dichloro-6-methyl-5-nitropyrimidine (6·4 g.), b. p. 137°/23 mm., m. p. 53—54·5° after crystallisation from light petroleum (lit., m. p., 53—54·5°), and (ii) a fraction, b. p. 188°/2 mm., which solidified on cooling. The latter substance separated from alcohol (10 c.c.) in yellow columnar prisms (0·75 g.), m. p. 111—113°, resolidifying to melt at 127°. It was dried *in vacuo* at 100° over phosphoric oxide for 6 hours after which treatment there was no sintering on immersion in a bath at 120° and the pure 2(4)-*chloro-6-methyl-4(2)-methylanilino-5-nitropyrimidine* had m. p. 128°; the substance slowly sublimed during the drying (Found: C, 52·2; H, 4·2; N, 19·7; Cl, 13·1. $C_{12}H_{11}O_2N_4Cl$ requires C, 51·7; H, 4·0; N, 20·1; Cl, 12·7%).

5-Amino-4-methylpyrimidine (XXII).—2 : 4-Dichloro-6-methyl-5-nitropyrimidine was reduced with zinc powder and boiling water to 5-amino-2-chloro-4-methylpyrimidine in the manner described by Gabriel and Colman (*Ber.*, 1901, **34**, 1250), and the crude product, m. p. 87°, was used directly. A solution of 5-amino-2-chloro-4-methylpyrimidine (2·7 g.) in water (30 c.c.) was shaken at 55° with 1·2% palladised strontium carbonate (0·5 g.) in hydrogen at atmospheric pressure until no further absorption took place (*ca.* 7 hours). The filtered solution was treated with sodium hydrogen carbonate and evaporated to dryness. The residue was extracted with boiling ethanol and the extract was evaporated to dryness. The halogen-free product was then purified by extraction with benzene, sublimation in a vacuum and crystallisation from benzene giving pure 5-amino-4-methylpyrimidine (1 g.) m. p. 150—151·5°; Gabriel and Colman (*locc. cit.*) record m. p. 152—153°.

2 : 4-*Bisamidinothio-6-methylpyrimidine Dihydrochloride and* 2 : 4-*Dithio-6-methyluracil.*—A solution of 2 : 4-dichloro-6-methylpyrimidine (3·26 g.) and thiourea (3·04 g.) in ethanol (50 c.c.) was refluxed for 1·5 hours, after which the reaction for thiourea with ammoniacal silver nitrate solution had become minimal. After cooling, the product (4·93 g.) was removed and treated with cold dilute hydrochloric acid (25 c.c.). The yellow insoluble portion (2·7 g.) was dissolved in aqueous potassium hydroxide and reprecipitated by the addition of acetic acid (cf. Gabriel and Colman, *Ber.*, 1899, **32**, 2922), giving 2 : 4-dithio-6-methyluracil (1·5 g.), m. p. above 380°, with discoloration from 250° to 260° (Found: C, 38·5; H, 3·9. Calc. for $C_5H_6N_2S_2$: C, 38·0; H, 3·8%). Gabriel and Colman (*locc. cit.*) record m. p. >280°.

The above dilute hydrochloric acid washings were evaporated to dryness in a vacuum at 40—50°, leaving a colourless crystalline residue (1·91 g.). It was dissolved in boiling methanol (25 c.c.) and treated with hot ethyl acetate (25 c.c.). When cold, the colourless crystals of pure 2 : 4-bisamidinothio-6-methylpyrimidine dihydrochloride (1·67 g.) were collected, m. p. 260° (decomp.) with pink coloration at 185—190° (Found, on material dried *in vacuo* over silica gel for 48 hours: C, 25·3; H, 4·3; N, 25·3. Calc. for $C_7H_{10}N_6S_2,2HCl,H_2O$: C, 25·2; H, 4·2; N, 25·2%). Polonovski and Schmitt (*Compt. rend.*, 1950, **230**, 754) record m. p. *ca.* 285° (decomp.) for this dihydrochloride and m. p. *ca.* 240° for the derived 2 : 4-dithio-6-methyluracil..

The dihydrochloride was very soluble in water and, on boiling, an aqueous solution readily decomposed to give the dithiouracil.

4-Methylpyrimidine (XXIII).—This was prepared (Gabriel and Colman, *Ber.*, 1899, **32**, 1534) by the action of zinc powder and boiling water on 2 : 4-dichloro-6-methylpyrimidine. Some 2-chloro-4-methylpyrimidine was obtained as a by-product. 4-Methylpyrimidine was finally purified by fractionation and had b. p. 86°/114 mm., n_D^{20} 1·4916.

1 : 3 : 6-*Trimethyluracil* (XXIX; R = Me).—This substance was obtained in excellent yield by methylation of 6-methyluracil with methyl sulphate, following the conditions adopted by Davidson and Baudisch (*J. Amer. Chem. Soc.*, 1926, **48**, 2379), in the case of uracil; it had m. p. 113° (lit., 111—112°).

2-*Methoxy-6-methyl-4-pyrimidone* (XXVIII; R = R′ = Me).—This compound was prepared by Bruce's method (*J. Amer. Chem. Soc.*, 1904, **26**, 454) with slight modifications. The product, which

separated from alcohol in colourless flattened prisms, had m. p. 207°, as recorded by Bruce, only on rapid heating, otherwise molecular rearrangement took place with fusion at 195°, followed by resolidification (Found: C, 52·1; H, 5·7; OMe, 21·5. Calc. for $C_9H_9O_2N_3$: C, 51·4; H, 5·7; OMe, 22·1%).

Physical Measurements.—(a) pK_a *values.* The compound (1 millimol.) was dissolved in N/20-hydrochloric acid (20 c.c.). The pH of the solution was measured (Cambridge pH-meter), and measured after every addition of 0·1 c.c. during titration with N-sodium hydroxide. The pK_a was calculated from each pH reading, taking into account the strength of the solution. In the case of compounds isolated as the hydrochlorides, these were dissolved in water before titration. Owing to its sparing solubility five times the above dilution was used for (XII), and the solution in alkali was titrated with acid.

(b) *Light absorption.* Light-absorption measurements were made with the Beckman D.U. quartz spectrophotometer at the pH values recorded in the Table. The buffer solutions used were: acetate (pH 4·7), phosphate (pH 7·0), glycine–sodium hydroxide (pH 11·0), together with N- (pH 0) and N/10-hydrochloric acid (pH 1·0) and N/10-sodium hydroxide (pH 13).

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[*Received, November 16th,* 1950.]

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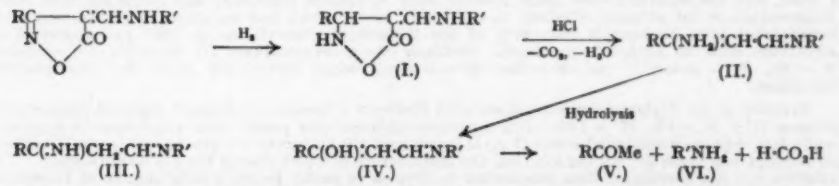
225. iso*Oxazolones. Part II.* iso*Oxazolidones.*

By G. SHAW.

The compounds formerly regarded as arylaminomethyl*iso*oxazolones (*J.*, 1950, 720) have now been shown to be arylaminomethylene*iso*-oxazolidones. The latter when treated with hydrogen chloride in acetic acid afforded anils of substituted β-amino-acraldehydes (II). Similarly the product of the palladium-catalysed reduction of 4-benzylidene-3-methyl-*iso*oxazol-5-one with hydrogen chloride afforded 3-imino-1-phenylbutene, suggesting the formation of an *iso*oxazolidone which however was not isolated. *iso*Oxazolones under the same conditions did not react with hydrogen chloride.

IN a preliminary paper (*J.*, 1950, 720), which is regarded as Part I of this series, it was shown that hydrogenation of the *iso*oxazolone nucleus produces a reactive anhydride-like compound postulated as an *iso*oxazolidone; this postulate has now been confirmed. It has been found that the compounds formerly assumed to be arylaminomethyl*iso*oxazolones are in fact aryl-aminomethylene*iso*oxazolidones (I), since hydrolysis afforded the arylamine in good yield. In addition when a solution of (I; R = R′ = Ph), (I; R = Me, R′ = Ph), (I; R = CH_2Ph, R′ = Ph), or (I; R = Me, R′ = *o*-tolyl) in dry acetic acid was saturated with dry hydrogen chloride at room temperature, evaporation of the solvent afforded the yellow crystalline hydrochloride of the base (II). The hydrochlorides of (I) were obtained as white solids by triturating the *iso*oxazolidones with hydrochloric acid.

The free bases (II; R = R′ = Ph) and (II; R = CH_2Ph, R′ = Ph) were precipitated as crystalline solids when aqueous solutions of the corresponding hydrochlorides were treated with sodium hydrogen carbonate solution, whereas the bases (II; R = Me, R′ = Ph) and (II; R =

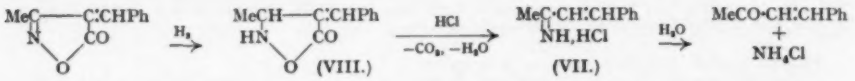


Me, R′ = *o*-tolyl) were obtained as oils. Ethereal solutions of the bases with hydrogen chloride gave precipitates of the unchanged salts.

That the bases were anils of substituted β-aminoacraldehyde (II) followed from their hydrolysis, which afforded the ketones (V), the amines (VI), and ammonia. The analogous

keto-anils (IV) are known to hydrolyse in a similar manner (Claisen and Fischer, *Ber.*, 1888, **21**, 1136). The alternative imino-structure (III) for the bases is unlikely since compounds of this type are generally very unstable in the presence of water.

When the product from the palladium-catalysed hydrogenation of 4-benzylidene-3-methyl-*iso*oxazol-5-one was treated with dry hydrogen chloride in acetic acid a white crystalline hydrochloride was obtained. This was soluble in water giving a clear solution which after 2—3 minutes became turbid and deposited a crystalline precipitate of benzylideneacetone. The hydrochloride readily evolved ammonia when treated with cold sodium hydroxide solution, and can be formulated as the imine (VII).



Neither 4-benzylidene- nor 4-benzyl-3-methyl*iso*oxazol-5-one showed any signs of reaction with dry hydrogen chloride under the conditions used for the corresponding *iso*oxazolidones, hence the imine (VII) must have arisen from a precursor, such as the *iso*oxazolidone (VIII) which has not yet been isolated in crystalline form.

The complete hydrogenation of 4-benzylidene-3-methyl*iso*oxazol-5-one to 4-phenylbutan-2-one and of 4-anilinomethylene-3-methyl*iso*oxazol-5-one to 4-anilinobutan-2-one has been dealt with previously (cf. Part I). It would thus appear that hydrogenation of the *iso*oxazolone nucleus results first in the saturation of the endocyclic double bond to afford an *iso*oxazolidone with anhydride properties which are stabilised by an exocyclic double bond in the 4-position. Saturation of the exocyclic double bond then results in the formation of a reactive system which combines readily with water or alcohol (cf. Part I). Initial saturation of the exocyclic double bond may also occur to a small extent since a low yield of 4-benzyl-3-methyl*iso*oxazol-5-one was obtained by hydrogenation of 4-benzylidene-3-methyl*iso*oxazol-5-one (Part I).

The anils (II) inhibited the growth of *Staphylococcus aureus* at a dilution of about 1 in 20,000.

Experimental.

4-Anilinomethylene-3-benzylisooxazolid-5-one (I; R = Ph·CH$_2$, R′ = Ph).—4-Anilinomethylene-3-benzyl*iso*oxazol-5-one (2 g.) was reduced with hydrogen and 5% palladium–charcoal for 1 hour (Uptake, 170 ml. Calc. for 1 mol., 161 ml.). Evaporation of the filtered solution *in vacuo* gave *4-anilinomethylene-3-benzylisooxazolid-5-one* (2 g.) which separated from water as very pale yellow needles, m. p. 166—168° (decomp.) (Found: N, 9·7. $C_{17}H_{16}O_2N_2$ requires N, 10%). The *iso*oxazolidone (0·5 g.) was triturated with 2N-hydrochloric acid (5 ml.), giving the *hydrochloride* (0·35 g.), which separated from ethanol–ether as white needles, m. p. 170°, sparingly soluble in water (Found: N, 8·8. $C_{17}H_{16}O_2N_2$.HCl requires N 8·85%).

4-Anilinomethylene-3-phenylisooxazolid-5-one (I; R = R′ = Ph).—4-Anilinomethylene-3-phenyl*iso*oxazol-5-one (2 g.) when similarly reduced gave *4-anilinomethylene-3-phenylisooxazolid-5-one* (2 g.) which separated from water as fine pale yellow needles, m. p. 170° (Found: C, 72·0; H, 5·45; N, 10·35. $C_{16}H_{14}O_2N_2$ requires C, 72·2; H, 5·3; N, 10·5%).

3-Methyl-4-m-toluidinomethyleneisooxazolid-5-one (I; R = Me, R′ = *m*-tolyl).—This product separated from water in pale yellow needles of the *monohydrate*, m. p. 98—100° (decomp.) (Found: N, 12·1. $C_{12}H_{14}O_2N_2.H_2O$ requires N, 11·85%).

Hydrolysis of the Arylaminomethyleneisooxazolidones.—The *iso*oxazolidones (I; R = R′ = Ph; R = Me, R′ = Ph; R = Ph·CH$_2$, R′ = Ph) (2 g.) were refluxed with N-hydrochloric acid (20 ml.) for 1 hour, and the solutions were made alkaline with 5N-sodium hydroxide and extracted with ether. Evaporation of the extracts afforded, in each case, an oil which had an odour of aniline and when benzoylated gave benzanilide (60—80% of the theoretical amount), m. p. 160° not depressed on admixture with an authentic specimen. Similarly the *iso*oxazolidones (I; R = Me, R′ = *o*-tolyl; R = Me, R′ = *m*-tolyl; and R = Me, R′ = *p*-tolyl) when hydrolysed gave the corresponding toluidines.

Reaction of the Arylaminoisooxazolidones with Hydrogen Chloride.—*1-Amino-1-phenyl-3-phenyliminopropene* (II; R = Ph, R′ = Ph). Dry hydrogen chloride was passed into a solution of 4-anilinomethylene-3-phenyl*iso*oxazolid-5-one (3 g.) in acetic acid (20 ml.) until the gas was no longer absorbed; no attempt was made to cool the solution, the temperature of which rose as the gas was absorbed. The solution was left overnight, then evaporated to dryness *in vacuo*, giving a solid residue of *1-amino-1-phenyl-3-phenyliminopropene hydrochloride* (2·2 g.) which separated from ethanol–ether as yellow needles, m. p. 210° (decomp.) (Found: C, 69·3; H, 6·0; N, 10·4. $C_{15}H_{14}N_2$.HCl requires C, 69·6; H, 5·85; N, 10·8%). The hydrochloride (1 g.) in water (20 ml.) was treated with excess of sodium hydrogen carbonate solution whereupon a yellow precipitate was obtained; the *1-amino-1-phenyl-3-phenyliminopropene* (0·8 g.) separated from light petroleum as bright-yellow plates, m. p. 167° [Found: C, 80·85;

H, 6·6; N, 12·8%; *M* (Rast), 217. $C_{18}H_{14}N_2$ requires C, 81·05; H, 6·35; N, 12·6%; *M*, 222]. A solution of the base (0·1 g.) in ether when treated with dry hydrogen chloride gave a precipitate of the hydrochloride, m. p. 210° (decomp.) not depressed on admixture with the sample prepared as above.

Hydrolysis of the imine. The base (2 g.) was refluxed with N-hydrochloric acid (20 ml.) for 30 minutes, and the cooled solution extracted with ether. Evaporation of the extract gave acetophenone (2 : 4-dinitrophenylhydrazone, m. p. 249—250° not depressed when mixed with an authentic specimen, m. p. 250°). The aqueous solution was concentrated to a small volume and made alkaline with 5N-sodium hydroxide; ammonia was evolved and was removed by aeration. The solution was shaken with benzoyl chloride giving benzanilide, m. p. 160° not depressed on admixture with an authentic specimen.

1-*Amino*-1-*methyl*-3-*phenyliminopropene* (II; R = Me, R′ = Ph).—4-Anilinomethylene-3-methyl-*iso*oxazolid-5-one (2 g.) when treated with hydrogen chloride as above gave 1-*amino*-1-*methyl*-3-*phenyliminopropene hydrochloride dihydrate* (1·55 g.) which separated from ethanol–ether as bright-yellow needles, m. p. 98—99° (decomp.) (Found: C, 52·4; H, 7·5; N, 12·2. $C_{10}H_{12}N_2$,HCl,$2H_2O$ requires C, 52·15; H, 7·35; N, 12·05%). Basification of a solution of the hydrochloride gave an oil which did not crystallise; a solution of the oil in ether, however, when treated with hydrogen chloride, gave the unchanged salt. Hydrolysis of the hydrochloride with acid gave acetone, ammonia, and aniline.

1-*Amino*-1-*benzyl*-3-*phenyliminopropene* (II; R = Ph·CH_2, R′ = Ph).—4-Anilinomethylene-3-benzyl-*iso*oxazolid-5-one (2 g.) with hydrogen chloride gave 1-*amino*-1-*benzyl*-3-*phenyliminopropene hydrochloride hydrate* (1·4 g.) which separated from ethanol–ether as yellow needles, m. p. 98—100° (decomp.) (Found: C, 65·95; H, 7·0; N, 9·5. $C_{16}H_{16}N_2$,HCl,H_2O requires C, 66·1; H, 6·6; N, 9·65%). Basification of an ice-cold aqueous solution of the hydrochloride (1 g.) with sodium hydrogen carbonate gave 1-*amino*-1-*benzyl*-3-*phenyliminopropene* (0·6 g.) as a crystalline precipitate which separated from a small amount of light petroleum on cooling to 0° as very pale yellow laths, m. p. 39—40° (Found: C, 81·1; H, 7·0; N, 12·0. $C_{16}H_{16}N_2$ requires C, 81·35; H, 6·8; N, 11·85%). Hydrolysis of the base with dilute acid gave benzyl methyl ketone, ammonia, and aniline.

1-*Amino*-1-*methyl*-3-*o-tolyliminopropene* (II; R = Me, R′ = *o*-tolyl).—3-Methyl-4-*o*-toluidinomethylene-*iso*oxazolid-5-one (10 g.) with hydrogen chloride gave 1-*amino*-1-*methyl*-3-*o-tolyliminopropene hydrochloride* (7 g.) which separated from ethanol–ether as pale yellow needles, m. p. 160° (Found: N, 13·35. $C_{11}H_{14}N_2$,HCl requires N, 13·3%). Hydrolysis of the salt gave acetone, ammonia, and *o*-toluidine.

Reaction of the Reduction Product of 4-*Benzylidene*-3-*methyliso*oxazol-5-*one with Hydrogen Chloride.*—4-Benzylidene-3-methyl*iso*oxazol-5-one (3 g.) in dry acetic acid (30 ml.) was reduced with hydrogen and 5% palladium–charcoal (Uptake, 385 ml. Calc. for 1 mol., 375 ml.). Dry hydrogen chloride was passed through the filtered solution until the gas was no longer absorbed, and the solution was set aside overnight and then evaporated to dryness *in vacuo*, giving an oil which soon crystallised. 3-*Imino*-1-*phenylbut*-1-*ene hydrochloride hydrate* (1·1 g.) separated from ethanol–ether as white, hair-like needles, m. p. 61—62° (Found: N, 6·8. $C_{10}H_{11}N$,HCl,H_2O requires N, 7·0%). The hydrate lost water when heated at 56°/15 mm., to give a glass-like material which readily solidified when rubbed with moist ether affording the hydrated hydrochloride. The imine (0·4 g.) was dissolved in water (0·5 ml.) giving a clear solution which after a few minutes deposited a crystalline precipitate of benzylideneacetone (0·2 g.), m. p. 42° not depressed on admixture with an authentic specimen, m. p. 42°. The imine readily afforded ammonia when warmed with sodium hydroxide solution, and with semicarbazide it gave benzylideneacetone semicarbazone (as white plates from methanol), m. p. 184—185°, undepressed on admixture with an authentic specimen, m. p. 185°, obtained as laths from methanol; a solution of the plates gave laths when seeded therewith. After a few days the solid hydrochloride had crumbled to a white powder of benzylideneacetone and ammonium chloride.

Treatment of 4-*Benzyl*-3-*methyliso*oxazol-5-*one with Hydrogen Chloride.*—A solution of the *iso*oxazolone (2 g.) in dry acetic acid was saturated with dry hydrogen chloride at room temperature. After 3 days the solution was evaporated to dryness *in vacuo* giving the unchanged *iso*oxazolone (1·8 g.). Under the same conditions 4-benzylidene-3-methyl*iso*oxazol-5-one did not react with hydrogen chloride.

The author expresses his thanks to Dr. E. Challen for the semi-microanalyses.

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[*Received, November 29th*, 1950.]

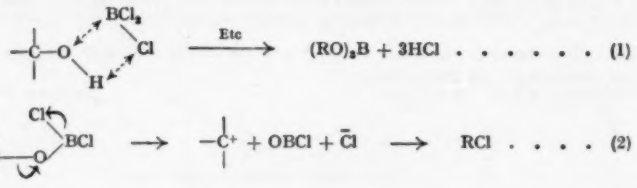
226. *Interaction of Boron Trichloride with Optically Active Alcohols and Ethers.*

By W. Gerrard and M. F. Lappert.

Boron trichloride and (+)-octan-2-ol gave (+)-tri-2-octyl borate and considerably racemised (−)-2-chloro-octane, the proportion of the latter increasing, so that it became the main product as the proportion of the trichloride was increased. Similarly (+)-1-phenylethanol afforded the (+)-1-chloro-1-phenylethane and (+)-tri-1-phenylethyl borate, completely racemised chloride being the main product when the proportion of the trichloride was increased. However, the trichloride readily caused racemisation of the 1-chloro-1-phenylethane itself. Both tri-esters readily interacted with the trichloride and afforded the corresponding alkyl chloride. Hydrogen chloride and hydrogen bromide were without action on the (+)-tri-2-octyl borate at 15°, but readily effected the dealkylation of (+)-tri-1-phenylethyl borate, the halide formed tending to have preponderantly retained configuration. (−)- and (±)-2-Chloro-octane and (±)-1-chloro-1-phenylethane were obtained by fission of the corresponding ethyl ethers, by means of the trichloride, the boron atom being found in the isolated ethoxyboron dichloride in both cases. Probable mechanisms are suggested.

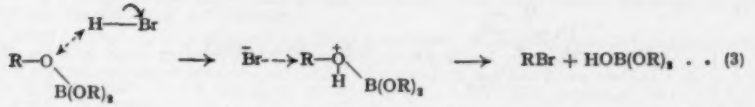
Successive replacement of the chlorine atoms in boron trichloride by interaction with methyl and ethyl alcohols at −60° was effected by Wiberg and Sütterlin (*Z. anorg. Chem.*, 1931, **202**, 1, 22, 31). Kinney, Thompson, and Cheney (*J. Amer. Chem. Soc.*, 1935, **57**, 2396) prepared di*iso*amyloxyboron chloride in 15% yield from the alcohol and trichloride, but by proportionation between the latter and tri-ester the yield was 45%.

A study of the interactions between boron trichloride and optically active alcohols has been undertaken in order to elucidate the nature and sequence of reactions occurring between alcohols and inorganic non-metallic halides. (+)-Octan-2-ol and (+)-1-phenylethanol were examined first, because the alcoholic carbon atom in the former may be considered as having a normal degree of reactivity, whereas in the latter the reactivity is much greater, owing to the polarisability of the phenyl group. Previous work shows that these alcohols are very convenient reference compounds. The results of our experiments are recorded in the table. There is a marked contrast between the reactions of (+)-octan-2-ol with boron trichloride, on the one hand, and with phosphorus halides (Gerrard, *J.*, 1944, 85; 1945, 848; 1946, 741) and silicon tetrachloride (Gerrard and Woodhead, *J.*, 1951, 519), on the other. With 3 mols. of (+)-alcohol to 1 mol. of trichloride the main product was (+)-tri-2-octyl borate and the subsidiary product was much-racemised (−)-2-chloro-octane, the latter becoming the main product as the relative proportion of trichloride was increased. The alkoxyboron chlorides, $B(OR)Cl_2$ and $B(OR)_2Cl$, could not be isolated.



The tri-ester was probably formed by three successive four-centre broadside approaches (1), whereas the formation of much racemised alkyl chloride was probably due to the pronounced electrophilic activity of the boron atom, further accentuated by the electron attraction of the chlorine atoms, as shown in (2). The greater the proportion of alcohol with respect to trichloride, the greater the chance that mechanism (1) will lead to the tri-ester. As hydrogen chloride failed to produce alkyl chloride when passed into the tri-ester, it is not likely to be responsible for formation of alkyl chloride in the alcohol–trichloride system. Furthermore, even hydrogen bromide at 100° did not react rapidly, and then the formation of 2-bromo-octane was accompanied by inversion without significant loss in rotatory power. The mechanism in

this case would appear to be that depicted in (3). Formation of much racemised (−)-2-chloro-octane from (+)-tri-ester and trichloride probably entails proportionation to the chloro-esters followed by decomposition according to (2).



(3)

Pyridine facilitated the broadside mechanism (1), presumably by virtue of the hydrogen bond, $RO{\cdot}H{\cdot\cdot}NC_5H_5$ (Gerrard, *J.*, 1939, 99); but in pentane solution the yield of (+)-tri-ester was only 64%, because some pyridine and trichloride were diverted to the complex, $Cl_3B{\cdot\cdot}NC_5H_5$. When the reagents were mixed in chloroform, however, the yield of tri-ester was increased to 85%. We conclude that this complex was not necessary for the production of tri-ester, because when the complex (prepared by mixing pyridine and the trichloride in pentane) was kept in pentane containing the requisite amounts of (+)-octan-2-ol and pyridine, there was a very slow conversion into pyridine hydrochloride even when the mixture was heated. The reagents (including the complex) being dissolved in chloroform, there was likewise a slow conversion at 15°; but after the mixture had been heated, the (+)-tri-ester was obtained in 84% yield. If, in the examples of certain alcohols, the tri-ester can be made more conveniently by boron

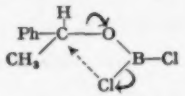
Reagents. (Numbers preceding formulæ refer to molecular proportions.)	Products.	Yield, %.	α_D.	Steric effect.*
R = 2-*Octyl*.				
3(+)-ROH (+7·7°), $1BCl_3$	(−)-RCl	9	−6·7°	I + much Ra
	(+)-$B(OR)_3$	83	+28·3	—
1 ,, ,, ,,	RCl	87	—	Ra
1 ,, ,, $2BCl_3$	(−)-RCl	97	−6·2	I + much Ra
3 ,, ,, $1BCl_3$ (with pyridine in pentane)	(+)-$B(OR)_3$	64	+28·0	—
Repeated in chloroform	,,	85	+28·0	—
3(+)-ROH (+3·1°), $1C_5H_5N{\cdot}BCl_3$, $2C_5H_5N$ in hot $CHCl_3$)	(+)-$B(OR)_3$	84	+11·9	—
(+)-$B(OR)_3$ (+28·0°), HBr (100°)	(−)-RBr	86	−37·4	I
,, ,, HI (15°)	(−)-RI	60	−45·2	I + some Ra
1(+)-$B(OR)_3$ (+30·0°), $1·9BCl_3$	(−)-RCl	93	−10·6	I + much Ra
1(+)-ROEt (+5·3°), $>1BCl_3$	(−)-RCl	98	− 3·1	I + much Ra
	$BCl_3{\cdot}OEt$	87	—	—
R = 1-*Phenylethyl*.				
3(+)-ROH (+21·6°), $1BCl_3$	(+)-RCl	50·1	+20·0	Re + Ra
	(+)-$B(OR)_3$	24·2	+21·6	—
1(+)-ROH (+32·4°), $1·2BCl_3$	RCl	87	—	Ra
3(+)-ROH (+28·4°), $1BCl_3$, $3C_5H_5N$ in pentane	(+)-RCl	—	+26·0	Re + Ra
	(+)-$B(OR)_3$	69	+28·0	—
3(+)-ROH (32·4°), $1BCl_3$, $3C_5H_5N$ in $CHCl_3$	(+)-$B(OR)_3$	86	+32·4	—
3(+)-ROH (+32·0°), $1C_5H_5N{\cdot}BCl_3$, $2C_5H_5N$ in hot $CHCl_3$	(+)-$B(OR)_3$	88	+29·8	—
(+)-$(RO)_2B$ (+31·0°), HCl	(+)-RCl	94	+13·0	Re + much Ra
,, (+30·0°), HCl (Repeat)	(+)-RCl	—	+8·0	Re + much Ra
+)-$(RO)_2B$ (+31·0°), HBr	(−)-RBr	74	−7·6	I + much Ra
,, (+30·0°), HBr (Repeat)	(+)-RBr	—	+2·4	Re + much Ra
(+)-$(RO)_2B$ (+28·0°), BCl_3	RCl	80	—	Ra
(+)-ROEt (+58·5°), BCl_3	RCl	—	—	Ra
	$BCl_3{\cdot}OEt$	78	—	—

* Re = retention. I = inversion of configuration. Ra = racemisation.

trichloride and pyridine than by reagents previously used, the complex would serve equally well, and would be a convenient form in which to store the trichloride.

With reference to (+)-1-phenylethanol, the special feature was the formation of (+)-1-chloro-1-phenylethane accompanied by some retention of configuration, when 1 mol. of trichloride was used for 3 mols. of alcohol. A suggested mechanism (4) is similar to that formulated for the formation of (+)-1-chloro-1-phenylethane from the (+)-alcohol through the agency of thionyl chloride (McKenzie and Clough, *J.*, 1913, **103**, 687), and designated S_Ni by Cowdrey, Hughes, Ingold, Masterman, and Scott (*J.*, 1937, 1252). Loss of rotatory power could be due to the concurrent operation of mechanism (2). It is clear that some molecules of the chloro-ester

react by continuation of mechanism (1), because the (+)-tri-ester was also isolated. As the proportion of trichloride was increased so the yield of alkyl chloride was increased, but racemisation became extensive. It is noteworthy that 1-chloro-1-phenylethane itself (in



$$\longrightarrow \quad RCl + OBCl \quad . \quad . \quad . \quad . \quad . \quad . \quad . \quad (4)$$

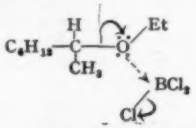
contrast to 2-chloro-octane) was readily racemised by the trichloride, presumably owing to the combined effect of the polarisability of the phenyl group and the electrophilic tendency of the boron atom, thus :

$$R\overset{\frown}{—}Cl\cdots\!\!>BCl_3 \longrightarrow \overset{+}{R} + \bar{C}lBCl_3 \longrightarrow \text{(racemised) } RCl + BCl_3.$$

(+)-Tri-1-phenylethyl borate was readily dealkylated by hydrogen chloride, and still more readily by hydrogen bromide, there being very considerable loss in activity, but a tendency towards preponderant retention of configuration. Values of rotatory power quoted in the table should be compared with the following maximum values (Gerrard, *loc. cit.*) for α_D^{18} (l = 10 cm.) : RCl, 99°; RBr, 131°.

Phenomena related to the formation of the complex, $Et_2O{\cdot}BCl_3$, and to its subsequent fission at the Et–O bond were described by Ramser and Wiberg (*Ber.*, 1930, **63**, 1136) and Wiberg and Sütterlin (*loc. cit.*). More recently, Benton and Dillon (*J. Amer. Chem. Soc.*, 1942, **64**, 1128) heated eight different ethers with boron tribromide and determined the fate of each hydrocarbon member of the ether. The mixed ethers with one exception were phenolic, and only one mol. of tribromide was used for three of the ether being treated. In our experiments we used more than one mol. of trichloride for each mol. of ether.

Ethyl (+)-2-octyl ether afforded ethoxyboron dichloride in 87%, and (−)-2-chloro-octane in 98% yield. Again, the mechanism must account for preponderant inversion with considerable loss in activity, and that suggested is shown in (5). It is clear that fission has occurred in accordance with the greater electron release of the secondary group. It is not surprising that ethyl (−)-1-phenylethyl ether afforded ethoxyboron dichloride and racemised 1-chloro-1-phenylethane.



$$\longrightarrow \quad EtO{\cdot}BCl_2 + \overset{+}{R} + \bar{C}l \quad \longrightarrow \quad RCl \quad . \quad . \quad . \quad (5)$$

The possibility should be borne in mind of a one-transition-state approach of the reagents, resulting in direct attachment of a chlorine atom to the reactive carbon atom. In these reactive systems, the energy possessed by the molecules at the moment of effective collision might influence the precise course of electronic rearrangement. The formation of an intermediate compound brings into play the consideration of the different ways in which it can effect the ultimate attachment of the chloride atom.

Experimental.

It is stated when reaction mixtures were treated with water. Rotatory powers are recorded for l = 10 cm.

Interaction of (+)-Octan-2-ol and Boron Trichloride.—The alcohol (4·8 g., 1 mol.; α_D^{15} +7·7°) was added dropwise to boron trichloride (1·8 g., 0·33 mol.) at −10°, and during the ensuing vigorous reaction hydrogen chloride (0·85 g.) was evolved. On distillation, (−)-2-chloro-octane (0·5 g.), b. p. 63°/16 mm., α_D^{15} −6·7° (Found : Cl, 23·8. Calc. for $C_8H_{17}Cl$: Cl, 23·9%), and *tri-2-octyl borate* (4·1 g.), b. p. 148°/0·5 mm., α_D^{15} +28·3°, n_D^{22} 1·4280, d_4^4 0·8642 (Found : C, 72·6; H, 12·6; B, 2·9. $C_{24}H_{51}O_3B$ requires C, 72·4; H, 12·8; B, 2·7%), were obtained. (+)-Octan-2-ol (1·2 g.), α_D^{15} +7·7°, was obtained from the tri-ester (1·43 g.) by steam-distillation in the presence of potassium hydroxide. In a similar way, 1 mol. of the trichloride and the alcohol (3·25 g., 1 mol.) afforded racemised 2-chloro-octane (3·2 g.), b. p. 60°/13 mm. (Found : Cl, 23·1%), and a residue which with water gave boric acid (1·30 g.) whereas, when 2 mols. of trichloride were used, the corresponding data were : 2-chloro-octane (3·6 g.), α_D^{15} −6·2° (Found : Cl, 23·6%), and boric acid (1·37 g.).

The trichloride (2·0 g., 1 mol.) in *n*-pentane (10 c.c.) was added to (+)-octan-2-ol (6·7 g., 3 mols.; α_D^{20} +7·7°) and pyridine (4·0 g.,3 mols.) in pentane (25 c.c.) at −10°. After 2 hours the white precipitate (5·2 g.) formed during the addition was separated and found to consist of pyridine hydrochloride (4·2 g.)

(Found : Cl, 30·5; C_5H_5N, 68·2. Calc. : Cl, 30·7; C_5H_5N, 68·4%) and a water-insoluble substance (1·0 g.), probably pyridine–boron trichloride, m. p. 115° (Found : Cl, 50·5; B, 6·5; C_5H_5N, 43·9%). On distillation, the pentane solution afforded pyridine (0·6 g.), b. p. 30°/20 mm., (+)-octan-2-ol (2·5 g.), b. p. 78°/15 mm., α_D^{20} +7·7°, and (+)-tri-2-octyl borate (4·3 g., 64%), b. p. 148°/0·5 mm., α_D^{20} +28·0° (Found : B, 2·72%). When the pentane filtrate was washed with water before distillation, the yield of tri-ester was reduced owing to hydrolysis.

We could find no way of purifying the substance we believe to be pyridine–boron trichloride, but by the interaction of boron trichloride and pyridine itself in pentane solution at −10° Dr. H. J. S. King obtained a white microcrystalline product which was doubtless *pyridine–boron trichloride*, m. p. 114·5—115° (Found : C, 30·6; H, 2·6; Cl, 53·8; N, 7·1; B, 5·7. C_5H_5N,BCl_3 requires C, 30·6; H, 2·6; Cl, 54·2; N, 7·1; B, 5·5%).

The yield of the tri-ester was increased to 85% by conducting the operation in chloroform, from which no precipitate was obtained when the trichloride (3·4 g., 1 mol.) was added to the (+)-alcohol (11·0 g., 3 mols.) and pyridine (6·7 g., 3 mols.) in the solvent (45 c.c. total volume) at −10°. The solid which remained on evaporation of the solvent in a vacuum at room temperature was leached with successive amounts of pentane, and the final residue (9·84 g.) consisted of pyridine hydrochloride (9·44 g.) and the water-insoluble substance (0·4 g.), m. p. 115°. Distillation of the pentane extract afforded octan-2-ol (1·5 g.), b. p. 78°/15 mm., and tri-2-octyl borate (9·4 g.), b. p. 148°/0·5 mm., α_D^{20} +28·0° (Found : C, 71·9; H, 13·0; B, 2·7. Calc. for $C_{24}H_{51}O_3B$: C, 72·4; H, 12·8; B, 2·72%).

Further to compare the effects of the two solvents mentioned, the reagents were mixed as described, and after the stated time the solvent was removed in a vacuum at room temperature. The solid residue was transferred to a sintered-glass crucible and extracted with water. The chloride ion found in the extract being assumed to be equivalent to pyridine hydrochloride, and this equivalent to the tri-ester produced, we concluded that in pentane the yield of tri-ester was 76·1% after 2 hours, and 79·5% after 24 hours; in chloroform solution, the yield was 90·9 after 2 hours, and 91·8% after 48 hours.

Interaction of Pyridine–Boron Trichloride and Octan-2-ol in the Presence of Pyridine.—(+)-Octan-2-ol (4·42 g., 3 mols.; α_D^{20} +3·1°), pyridine (1·78 g., 2 mols.), and pyridine–boron trichloride (2·21 g., 1 mol.) (prepared from pyridine and the trichloride) were heated under reflux in chloroform solution for 4 hours. After removal of the solvent in a vacuum, the residue was leached with pentane, and the final solid residue consisted of pyridine hydrochloride (3·87 g.) (Found : Cl, 30·1; C_5H_5N, 68·0%) and unchanged boron complex (0·1 g.), m. p. 114°. On distillation, the pentane solution afforded (+)-octan-2-ol (0·2 g.), α_D^{20} +3·1°, and (+)-tri-2-octyl borate (3·8 g.), b. p. 156°/1 mm., α_D^{20} +11·9° (Found : C, 72·7; H, 13·0; B, 2·70%). When the reagents were kept in chloroform at room temperature, the conversion into tri-ester was very slow—only 1% in 48 hours. In pentane the conversion was slow; even after the mixture had been heated under reflux for 6 hours the yield was only 9·8%.

Interaction of Boron Trichloride and 1-Phenylethanol.—The trichloride (2·0 g., 1 mol.) in pentane (10 c.c.) was added to (+)-1-phenylethanol (6·1 g., 3 mols.; α_D^{20} +21·6°) in pentane (10 c.c.) at −10°. Some unreacted alcohol separated, but when the mixture was shaken at room temperature the separate layer disappeared, a precipitate formed, and hydrogen chloride was evolved. On distillation, (+)-1-chloro-1-phenylethane (3·6 g.), b. p. 76°/14 mm., α_D^{20} +20·0° (Found : Cl, 25·0. Calc. : Cl, 25·3%), (probably) (+)-di-1-phenylethyl ether (0·7 g.), b. p. 110°/0·3 mm., α_D^{20} +56·8° (Found : C, 85·5; H, 7·9. Calc. for $C_{16}H_{18}O$: C, 85·0; H, 8·0%), and (+)-tri-1-phenylethyl borate (1·5 g.), b. p. 174°/0·2 mm., α_D^{20} +21·6° (Found : B, 2·84. Calc. : B, 2·89%) (see later), were obtained. When 1·2 mols. of trichloride and 1·0 mol. of alcohol, α_D^{20} +32·4°, were used, racemised 1-chloro-1-phenylethane (87% yield), b. p. 77°/18 mm. (Found : Cl, 25·1%), was obtained.

It was shown that 1-chloro-1-phenylethane is readily racemised in contact with boron trichloride. After the former, α_D^{20} +27·6° (3·0 g.), had been in contact with the latter (1·8 g.) in pentane (10 c.c.) for 1 hour at 15°, (±)-1-chloro-1-phenylethane (2·9 g., 97%), b. p. 80°/20 mm. (Found : Cl, 25·4%), was isolated. Under similar conditions, even after 24 hours, (+)-2-chloro-octane showed no change in rotatory power.

Boron trichloride (3·5 g., 1 mol.) in pentane (10 c.c.) was added to (+)-1-phenylethanol (10·5 g., 3 mols., α_D^{20} +28·4°) and pyridine (6·9 g., 3 mols.) in pentane (35 c.c.) at −10°. After 4 hours at 15°, a lower semi-solid layer was washed with ether, the washings being added to the upper layer, and the solid residue consisted of pyridine hydrochloride (6·4 g.) (Found : Cl, 30·0; C_5H_5N, 67·8%) and pyridine–boron trichloride (0·3 g.), m. p. 115°. From the ethereal solution, (+)-1-chloro-1-phenylethane (2·5 g.), b. p. 80°/20 mm., α_D^{20} +26·0° (Found : Cl, 25·0%), (+)-1-phenylethanol (2·0 g.), b. p. 90°/20 mm., α_D^{20} +28·3°, and (+)-*tri-1-phenylethyl borate* (7·2 g., 69%), b. p. 175°/0·5 mm., α_D^{20} +28·0° (Found : C, 77·7; H, 7·7; B, 2·85. $C_{24}H_{27}O_3B$ requires C, 77·0; H, 7·2; B, 2·87%), were obtained. When the operation was conducted in chloroform, the tri-ester, b. p. 170—174°/0·4 mm., α_D^{20} +32·8° (from alcohol; α_D^{20} +32·4°) (Found : C, 77·2; H, 7·5; B, 2·96%), was obtained in 86% yield.

On steam-distillation from an aqueous solution of potassium hydroxide, the (+)-alcohol (0·9 g.), α_D^{20} +32·1°, was obtained from the tri-ester (1·076 g.), α_D^{20} + 32·8°.

As described above, pyridine–boron trichloride (1.706 g., 1 mol.), pyridine (1·37 g., 2 mols.), and (+)-1-phenylethanol (3·18 g., 3 mols.; α_D^{20} +32·0°) were heated under reflux in chloroform (15 c.c.) for 3 hours. The solvent was evaporated in a vacuum, and the final residue after extraction with pentane was pyridine hydrochloride (2·97 g.) (Found : Cl, 30·5; C_5H_5N, 68·2%). Distillation of the pentane solution afforded (+)-tri-1-phenylethyl borate (2·8 g., 88%), b. p. 173°/0·2 mm., α_D^{20} +29·8° (Found : B, 2·86%).

Interaction of Hydrogen Halides and Tri-esters.—Tri-2-octyl borate was recovered unchanged in amount and rotatory power after hydrogen chloride had been passed into it for 2 hours at 15°. Similarly, hydrogen bromide had no noticeable action at this temperature, but when passed for at least 16 hours

at 100—110° it afforded (−)-2-bromo-octane (3·8 g.) (from 3·10 g. of tri-ester, a_D^{20} +28·0°), b. p. 74°/15 mm., a_D^{20} −37·4° (Found: Br, 41·4. Calc.: Br, 41·4%). When hydrogen iodide was passed into the tri-ester (1·32 g.) for 5 hours at 15°, (−)-2-iodo-octane (1·4 g.), b. p. 85°/15 mm., a_D^{20} −45·2° (Found: I, 51·8. Calc.: I, 52·9%), was formed.

Boric acid was precipitated when dry hydrogen chloride was passed into (+)-tri-1-phenylethyl borate (1·9 g., a_D^{20} +31·0°) for 3 hours at 15°. (+)-1-Chloro-1-phenylethane (2·0 g., 94%), b. p. 68—69°/10 mm., a_D^{20} +13·0° (Found: Cl, 25·5. Calc.: Cl, 25·3%), and boric acid (0·310 g. Calc.: 0·310 g.) were isolated. In a similar way the same ester (1·41 g.) and hydrogen bromide afforded (−)-1-bromo-1-phenylethane (1·6 g.), b. p. 90°/15 mm., a_D^{20} −7·6° (Found: Br, 43·5. Calc.: Br, 43·3%), and a residue of boric acid (0·203 g.).

Interaction of Trichloride and Tri-esters.—(+)-Tri-2-octyl borate (2·3 g., 1 mol.; a_D^{20} +30·0°) (from the alcohol, a_D^{20} +7·96°) in pentane (5 c.c.) was added to the trichloride (1·3 g., 1·9 mols.) in pentane (5 c.c.) at −10°. From the mixture, (−)-2-chloro-octane (2·4 g., 93%), b. p. 59—60°/13 mm., a_D^{20} −10·6° (Found: Cl, 23·8. Calc.: Cl, 23·9%), was obtained. Similarly, completely racemised 1-chloro-1-phenylethane (2·8 g.), b. p. 77°/15 mm. (Found: Cl, 25·4%), was obtained from the tri-ester (2·8 g., 1 mol.; a_D^{20} +28·0°) and the trichloride (1·8 g., 2 mols.).

Interaction of Boron Trichloride with Ethyl (+)-1-Phenylethyl Ether.—(−)-1-Chloro-1-phenylethane, a_D^{20} −86·6° (Gerrard, *J.*, 1946, 741), was converted into the ether, b. p. 76—78°/20 mm., a_D^{20} +58·5° (Found: C, 80·4; H, 9·5. Calc. for $C_{10}H_{14}O$: C, 80·0; H, 9·4%), by Hughes, Ingold, and Scott's method (*J.*, 1937, 1201). The ether (3·3 g., 1 mol.) was added to the trichloride (2·6 g., 1 mol.) at −10°. After one hour distillation afforded ethoxyboron dichloride (2·2 g., 78%), b. p. 78—80° (Found: Cl, 55·3; B, 8·52. Calc. for $C_2H_5OCl_2B$: Cl, 55·9; B, 8·53%), and a residue (2·8 g.) which was mixed with water and extracted with ether. From the dried ethereal extract, completely racemised 1-chloro-1-phenylethane (1·0 g.), b. p. 74°/12 mm. (Found: Cl, 25·0%), and a non-distillable oil (1·6 g.) were obtained.

The trichloride (5·0 g., >1 mol.) and ethyl (+)-2-octyl ether (2·6 g.; a_D^{20} +5·3°; prepared by Kenyon and McNicol's Method, *J.*, 1923, **123**, 14) were mixed at −10°, and the mixture was set aside for 2 hours. Distillation afforded ethoxyboron dichloride (1·8 g., 87%), b. p. 78—80° (Found: Cl, 56·1; B, 8·53. Calc. for $C_2H_5OCl_2B$: Cl, 55·9; B, 8·53%), and (−)-2-chloro-octane (2·8 g., 98%), b. p. 60—61°/13 mm., a_D^{20} −3·1° (Found: Cl, 23·6. Calc.: Cl, 23·9%).

The authors thank the Chemical Society for a grant from the Research Fund, and one of them (M. F. L.) thanks the D.S.I.R. for a personal grant.

THE NORTHERN POLYTECHNIC, HOLLOWAY ROAD, N.7. [*Received, December 9th*, 1950.]

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227. *The Colour of Organic Compounds. Part I. A General Colour Rule.*

By EDWARD B. KNOTT.

Förster's colour rule (*Z. Elektrochem.*, 1939, **45**, 548) has been modified to cover non-ionic as well as ionic dyes. An empirical method is given to allow the rule to be applied by organic chemists. It is also shown that this rule can be re-stated in terms consistent with the conclusions of Kuhn (*J. Chem. Physics*, 1949, **17**, 1198) from the electron-gas model.

THE closely related colour rules of Lewis and Calvin (*Chem. Rev.*, 1939, **25**, 273) and of Lewis (*J. Amer. Chem. Soc.*, 1945, **67**, 770) are the only ones which have been applied to predict the effect, on the light absorption of a dye, of a structural change at a point in the molecule lying between the auxochromes.* These rules have been found to be unreliable in a number of cases (see later) because they neglect the position of the point of the change in relation to the terminal $\pm M$ atoms and also because they assume that, in an ionic dye, each atom of the chromophoric chain must carry a fractional charge of the same sign as that of the characteristic charge. Moreover, by their definition, they cannot be applied to non-ionic (electrically neutral) molecules. Brooker (with Sklar, *Rev. Mod. Physics*, 1942, **14**, 279) also evolved a rule which might conceivably be applied to such structural changes. It has never been

* Since the original draft of this paper was submitted in March 1950 a further number of generalizations of this type have been given by Dewar (*J.*, 1950, 2329).

exemplified (the difference in absorption of the two dyes given in that article being caused, it is considered, by an extra-conjugation effect) largely because of the narrow field of its applicability.

It is the purpose of this paper to develop a general rule covering structural changes of this type which may be applied to dyes of any type. As a basis, a much neglected rule given by Förster (*loc. cit.*) is re-interpreted and a method evolved to enable an organic chemist to apply it.

The General Rule.—Förster's rule which can, by definition, only be applied to ionic dyes and which has never been exemplified, considers that $\lambda_{max.}$ of the dye will increase with a decreasing tendency of the chain of atoms (chromophores) lying between the auxochromes to take up the characteristic charge. Its identity with the later rule by Lewis (*loc. cit.*) is obvious. If it is accepted that the resultant charge distribution on the atoms of a resonance hybrid is determined by the relative contributions of all the participating structures, then in any such system the chromophoric atoms carry charges only in the excited structures. The Förster rule can accordingly be re-written in a form which allows its application to non-ionic dyes, namely, $\lambda_{max.}$ will increase as the contributions by any of the interauxochromic,* ionic excited structures decrease. Since the contributions by the various structures depend largely on their relative energies it follows that $\lambda_{max.}$ will be increased by raising the energy of any one interauxochromic, ionic, excited structure. These two derivations of the Förster rule will be referred to as the general rule. The relationship of this rule to the Brooker–Sklar rule, which is concerned with the general alteration in the level of all interauxochromic, excited structures, is clear.

Method of Application.—In order to apply this rule to specific examples it is necessary, in theory, to consider all the possible structures contributing to the hybrid and to assess the effect of a particular structural change on the significance of each structure. It will then be found that this change, in all cases, will increase the contributions of some structures and decrease those of others. Since, therefore, in all cases, the change in $\lambda_{max.}$ following a structural change is a resultant of both hypsochromic and bathochromic shifts a very complicated and tedious procedure is involved because of the absence of quantitative data. The process can, in practice, be simplified considerably by observing the following conditions.

First, it must be assumed that the more significant the structure undergoing a fixed energy change, or the greater the energy change in structures of equal significance resulting from the structural change, the greater will be the effect of that change on the absorption. Two " most likely," *i.e.*, most significant, structures are then selected in which the atom at which the structural change occurs is positively charged in one case and negatively charged in the other. These two structures are chosen, and their relative significance is assessed, by considering such criteria of energy as the number of covalent bonds, the degree of disruption of the conjugated system, the presence of aromaticity, charge separation, or adjacent atoms of like charge (cf. Wheland, " The Theory of Resonance," 1947, p. 15).

If there is a clear-cut difference between the assessed importance of these two structures then the direction of the resultant shift and, after experience, its approximate magnitude can be assessed. This requires the application of further criteria which will determine the direction of the change in the energy level of the more important structure; such criteria include stabilization by the formation of new resonance systems following the introduction of $\pm M$ atoms or groups or a change in the electronegativity of the atom replaced. The magnitude of the shift will in general be greater the larger the difference in the relative significance of the two chosen structures.

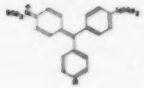
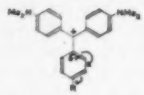
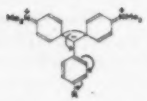
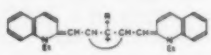
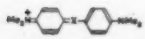
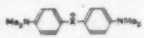
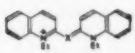
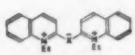
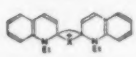
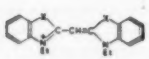
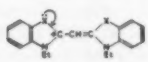
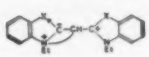
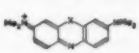
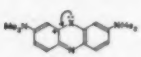
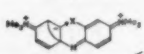
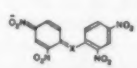
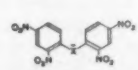
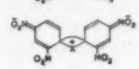
In view of the necessarily rough empiricism of the above procedure it is, none the less, surprising how reliable the rule has proved. The annexed tables give examples of various dye types which illustrate its working. The reason for the choice of the more significant structure of the two given for each dye and the effect of the structural change on its energy level is in most cases obvious from a consideration of the above criteria. For dyes (II) and (IV) the structures involving C^- are considered to be the more stable since, although charge separation is required for their contribution, they each contain two covalent bonds more than those structures involving C^+ and also contain fully aromatic quinoline nuclei. The introduction of a $+M$ group at C^- or a $-M$ group at C^+ will always give rise to a new resonance system with a consequent decrease in the energy of the system. Similarly, owing to the high electronegativity of nitrogen compared with carbon the replacement of ^-CH by N^- will also stabilize the system, whilst a similar replacement of ^+CH by N^+ will raise the energy of the system. The introduction

* " Interauxochromic " refers to those structures in which one or more of the atoms lying between the auxochromes is charged.

of a $+I$ atom or group at C^+ [*e.g.*, dye (II), less likely structure] or a $-I$ atom or group at C^- will also raise the energy of the structure (relative to the extreme structure) by increasing the amount of charge on the carbon atom. In dye (V) the energy increase is a result of the lower $-M$ effect of sulphur compared with that of oxygen.

It will be found that the Lewis–Calvin or the Lewis rule predicts bathochromic shifts for

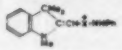
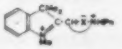
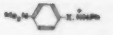
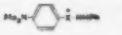
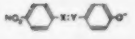
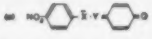
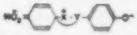
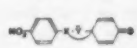
Energetically symmetrical ionic dyes.

	Dye and structural change.	Likely structures (more likely first).	Effect of change on energy level.*	Expected shift.†	Observed absorption.
(I.)			+	B	R = H 621 mμ. R = NO_2 646 mμ. Shift +25 mμ.
	R = H Change to R = NO_2		−	—	—
(II.)			−	H	R = H 708 mμ. R = NO_2 580 mμ. Shift −128 mμ.
	R = H Change to R = NO_2		+	—	—
(III.)			+	B	X = CH 603 mμ. X = N 725 mμ. Shift +122 mμ.
	X = CH Change to X = N		−	—	—
(IV.)			−	H	X = CH 522 mμ. X = N 424 mμ. Shift −98 mμ.
	X = CH Change to X = N		+	—	—
(V.)			+	B	R = O 372 mμ. R = S 442 mμ. Shift +70 mμ.
	X = O Change to X = S		−	—	—
(VI.)			−	H	R = H 725 mμ. R = S 665 mμ. Shift −60 mμ.
	X = –H H– Change to X = S		−	—	—
(VII.)			−	H	X = CH blue ‡ X = N red Shift, negative
	X = CH Change to X = N		+	—	—

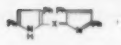
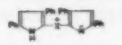
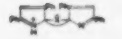
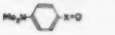
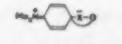
* + = increase; − = decrease. † B = bathochromic; H = hypsochromic.

‡ Wizinger, *J. pr. Chem.*, 1941, **157**, 129.

Energetically asymmetrical ionic dyes.

	Dye and structural change.	Likely structures (more likely first).	Effect of change on energy level.	Expected shift.	Observed absorption.
(VIII.)			+	B	X = CH 409 mμ. X = N 438 mμ. Shift +29 mμ.
	X = CH Change to X = N		−	—	—
(IX.)			+	B	X = CH 435 mμ. X = N 516 mμ. Shift +81 mμ.
	X = CH Change to X = N		−	—	—
(X.)			−	H	X = CH 437 mμ. X = N 406 mμ. Shift −31 mμ.
	X = Y = CH Change to (a) X = N, Y = CH (b) X = CH, Y = N		+	—	—
			+	B	Y = CH 437 mμ. Y = N 448 mμ. Shift +11 mμ.
			−	—	—

Non-ionic dyes.

	Dye and structural change.	Likely structures (more likely first).	Effect of change on energy level.	Expected shift.	Observed absorption.
(XI.)			+	B	X = CH 550 mμ.¶ X = N 614 mμ. Shift +64 mμ.
	X = CH Change to X = N		−	—	—
(XII.)			+	B	X = CH 342 mμ. X = N 423 mμ. Shift +81 mμ.
	X = CH Change to X = N		−	—	—
(XIII.)			+	B	X = CH 437 mμ. X = N 498 mμ. Shift +61 mμ.
	X = CH Change to X = N		−	—	—

The author thanks Dr. M. A. T. Rogers for samples of some of these dyes.

¶ In pyridine.

dyes (II) * and (IV). This failure which also occurs in many related dyes is believed to be caused by the unusually strong $-M$ effect of the heterocyclic rings which has the effect of building up a negative charge on certain chain atoms in spite of the positive nature of the characteristic charge.

It will be noted that the replacement of $-CH=$ by $-N=$ in these dyes may cause either a hypsochromic or a bathochromic shift. A simple rule which can be applied in these cases is that, if the carbon atom at which the replacement takes place is separated from the active $\pm M$ centres of the auxochromes by an odd number of conjugated atoms,† then a hypsochromic shift results whilst a separation by an even number of atoms results in a bathochromic shift.‡

* A bathochromic shift is also predicted by Dewar (*loc. cit.*, generalization 4).
† This generalization was reached also by Förster (*loc. cit.*).
‡ Cf. Dewar (*loc. cit.*), also Kuhn, *Chimia*, 1950, **9**, 203.

Application to the Electron-gas Model of Absorption.—Kuhn (*loc. cit.*) in applying the electron-gas model to the absorption of energetically unsymmetrical dyes regards the potential field of the conjugated system as approximating to a sine wave. A decrease in the amplitude of this wave resulting from decreasing non-degeneracy of the system results in a bathochromic shift. Similarly he suggests that even in symmetrical dyes the alternate bonds of the chromophoric system may not be quite of the same order since contributions to the hybrid by excited structures may disturb the uniformity. The conclusion can thus be drawn that for any particular length of conjugation the more uniform the potential field of the system the larger will be the calculated value of $\lambda_{max.}$.

In comparing the Förster and the general rule with the above it is at once clear that the smaller the tendency of the chromophoric atoms to take up the characteristic charge in ionic dyes, or the smaller the importance of the excited structures in dyes of any type, the smaller will be the

FIG. 1.

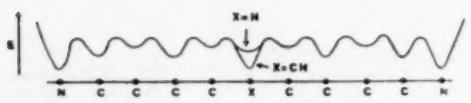
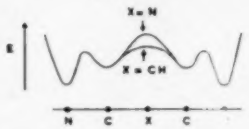


FIG. 2.



probability of variations in charge on the chromophoric atoms (and hence in potential field of these atoms) and, in symmetrical dyes, the smaller will be the disturbance in the uniformity of the bond order of alternate links.

Although, for his treatment, Kuhn regards the dyes as containing a uniformly fluctuating potential field it is clear that in certain cases this is not so. Thus dye (III) must contain a big dip in the field at the point X owing to the great significance of the excited structure containing X^+. On the other hand, in dye (IV) there must be a hump corresponding to the importance of structures containing X^-. The field diagrams of these dyes may be represented by Figs. 1 and 2. The replacement of X=CH by X=N in (III), and of X=N by X=CH in (IV), will then cause an increase in the uniformity of the field by reducing the irregularity as shown.

The conclusions to be drawn from the Förster and the general rule are thus seen to accord fully with the findings of Kuhn.

The author thanks Dr. W. E. Moffitt for helpful criticism.

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[*Received, August 12th,* 1950.]

228. *The Colour of Organic Compounds. Part II. Colour Phenomena of Bis-2-(3 : 5-diphenylpyrrole)methins.*

By R. A. JEFFREYS and E. B. KNOTT.

The abnormal colour changes shown on salt formation by *meso*-substituted bis-2-(3 : 5-diphenylpyrrole)methins are attributed to overcrowding and loss of nuclear planarity. The *meso*-alkyl dye bases are unstable and rapidly change into carbinol ethers in alcohol.

THE change in colour from red to green on acidification of solutions of bis-2-(3 : 5-diphenylpyrrole)*meso*phenylmethin (I; R = Ph) reported by Rogers (*J.*, 1943, 596) is very interesting in view of the relative insensitivity of the parent dye (I; R = H) to change in pH, solutions of the latter dye in pyridine or acetic acid being red. That this sensitivity is not caused by the presence of the *meso*phenyl group *per se* has now been shown by our finding that the dihydrochloride of (I; R = Me) and the monohydrochloride of (I; R = Et) give blue solutions, changing to red on basification. Unlike the phenyl compound the *meso*alkyl bases are unstable, readily giving the carbinol ethers in alcohol. The latter regenerate the dye salts on acidification (cf. Brunings and Corwin, *J. Amer. Chem. Soc.*, 1942, **64**, 593).

All these dye bases may be considered to have extreme structures (I*a*, *b*) of unequal energy whilst the cations of the dye salts formed by proton addition to (I) will be energetically symmetrical dyes of the cyanine type.

The bathochromic effect of the removal of non-degeneracy of a linear resonator is well established (Brooker and Sprague, *J. Amer. Chem. Soc.*, 1941, **63**, 3203, 3214; Schwarzenbach' *Z. Elektrochem.*, 1941, **47**, 40), so that proton addition to these dye bases should be bathochromic'

The Table shows the absorption figures of the dye bases and dye salts in carbon tetrachloride and acetic acid respectively. Stable solutions of (I; R = alkyl) were obtained by adding triethylamine to a solution of the salt in anhydrous solvent.

	Dye base.		Dye salt.			Dye base.		Dye salt.	
R in (I).	$\lambda_{max.}$ (mμ.).	$10^{-4}\varepsilon_{max.}$.	$\lambda_{max.}$ (mμ.).	$10^{-4}\varepsilon_{max.}$.	R in (I).	$\lambda_{max.}$ (mμ.).	$10^{-4}\varepsilon_{max.}$.	$\lambda_{max.}$ (mμ.).	$10^{-4}\varepsilon_{max.}$.
H	537	4·03	557	8·7	Me	550	0·74	595	3·75
Ph	546	3·15	616	4·2	Et	540	0·50	605	2·82

Figs. 1—3 are scale drawings of the dye bases or salts in which R = H, Ph, and Me, respectively. The parent base (R = H) is seen to be substantially free from crowding, and completely free if two of the phenyl residues rotate from coplanarity or bend outwards or if the bridge angle θ closes. The bathochromic shift of 20 mμ. and the doubling of the value for ε on proton addition is consistent with the loss of non-degeneracy and preservation of a planar structure in the dye salt.

FIG. 1.

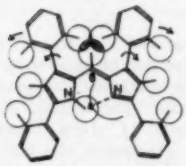

FIG. 2.

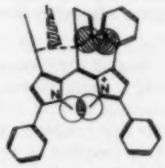

FIG. 3.

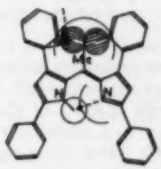

Fig. 2 shows severe overcrowding in (I; R = Ph), whether the top phenyl residues are coplanar or at right angles to the plane of the heterocyclic nuclei. The consequent distortion of the molecule can only be imagined but the decrease in $\varepsilon_{max.}$ (3·15 v. 4·03) indicates loss of nuclear (pyrrole) planarity. This must occur by the twisting of both bridge bonds. Since the base is non-degenerate the left-hand bridge bond will be of a lower order than the right hand one and as it is twisted so will its single-bond character increase. This will work hypsochromically by increasing the non-degeneracy of the system. On the other hand the twisting of the predominantly double bond will have the opposite effect (Brooker *et al.*, *Chem. Reviews*, 1948, **16**, 1124). The net result of these two factors might well explain the bathochromic shift of 9 mμ. observed on introduction of the *meso*phenyl group. Similar considerations apply for the *meso*alkyl group (Fig. 3); in this case the over-crowding is apparently even greater, as indicated by the low values for $\varepsilon_{max.}$.

The addition of a proton to these dyes with the consequent attainment of degeneracy results in the bridge bonds becoming of equal order. As Brunings and Corwin (*loc. cit.*) and Brooker *et al.* (*loc. cit.*) have shown, the twisting of adjacent bonds in a degenerate system results only in a bathochromic shift. The very large bathochromic shifts of 70, 45, and 65 mμ. in the three dyes on proton addition will thus be occasioned, first, by removal of non-degeneracy and, secondly, by twisting of both bridge bonds, there being in these cases no hypsochromic effect in action. The effect of the loss of nuclear planarity may also be seen by a comparison of $\varepsilon_{max.}$ of (I; R = H) with that of these dye salts.

EXPERIMENTAL.

(Microanalyses by Drs. Weiler and Strauss, Oxford. M. p.s are uncorrected.)

Bis-2-(3 : 5-*diphenylpyrrole*)*mesomethylmethin Dihydrochloride*.—2 : 4-Diphenylpyrrole (1 g.) and acetyl chloride (8 c.c.) were refluxed together for 10 minutes on the steam-bath. Part of the dye crystallized during this time. After chilling, the dye *salt* (0·8 g.) was collected and obtained as bronze plates, m. p. 202°, from alcoholic hydrogen chloride (Found: C, 77·0; H, 5·0; N, 4·9; Cl, 12·8. $C_{34}H_{28}N_2.2HCl$ requires C, 76·3; H, 5·25; N, 5·25; Cl, 13·3%).

Bis-2-(3 : 5-*diphenylpyrrole*)*mesoethylmethin Hydrochloride*.—2 : 4-Diphenylpyrrole (1 g.) and propionyl

chloride (8 c.c.) were refluxed together for 20 minutes on the steam-bath, and the dye ***hydrochloride*** was collected after chilling. It (0·75 g.) formed bronze plates, m. p. 190°, from alcoholic hydrogen chloride (Found: N, 5·1; Cl, 6·55. $C_{28}H_{27}N_3$,HCl requires N, 5·45; Cl, 6·9%).

1 : 1-*Di*-2-(3 : 5-*diphenylpyrryl*)*ethyl Ethyl Ether*.—Bis-2-(3 : 5-diphenylpyrrole)*meso*methylmethin dihydrochloride (2 g.) was dissolved in ethanol (20 c.c.), and a slight excess of anhydrous triethylamine was added. A deep red colour developed which became paler during 72 hours. The solution was then poured into water (100 c.c.), and the resulting *ether* collected, dried, and obtained as dark brown crystals, m. p. 178°, from *n*-hexane. It gave a yellow solution in alcohol (Found: C, 84·9; H, 6·5; N, 6·05. $C_{58}H_{52}ON_6$ requires C, 85·05; H, 6·3; N, 5·5%).

The authors are indebted to Misses A. Matthews and M. E. Cole for absorption measurements, to Mr. L. A. Williams for the preparation of the carbinol ether, and to Dr. M. A. T. Rogers for initial samples of dyes (I; R = H and Ph).

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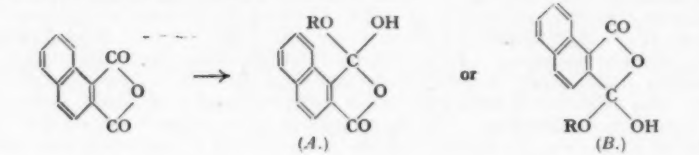
[*Received, August 12th*, 1950.]

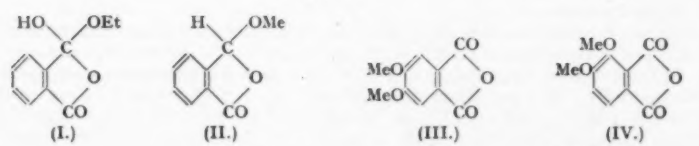
229. *The Action of Alcohol on Phthalic Anhydrides.*

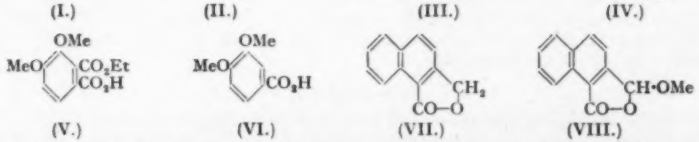
By YEHUDA HIRSHBERG, DAVID LAVIE, and ERNST D. BERGMANN.

By an analysis of the ultra-violet absorption spectra of the substances concerned and of related compounds of unambiguous structure, it is shown that phthalic anhydride, hemipinic anhydride, and naphthalenedicarboxylic anhydrides react with alcohols first by addition to the double bond of one of the CO groups. The hemiacetal-like substances thus formed isomerise gradually to the corresponding monoesters. 4 : 5-Dimethoxyphthalic anhydride forms the monoester almost instantaneously.

HIRSHBERG AND JONES (*Canad. J. Res.*, 1949, *B*, **27**, 437) have observed that the ultra-violet absorption spectra of naphthalene-1 : 2- and -2 : 3-dicarboxylic anhydride in alcoholic solution undergo a slow change, until eventually a stationary state is reached which differs significantly from the spectra of the same substances in non-alcoholic solvents. The change could be ascribed to a formation of hemi-esters and, indeed, Siegel and Moran (*J. Amer. Chem. Soc.*, 1947, **69**, 1457) have reported that this reaction is instantaneous. However, the validity of Siegel and Moran's interpretation has been refuted by Anderson and Kenyon (*ibid.*, 1948, **70**, 3952) and by Lavine and Herkness (*ibid.*, p. 3951). Hirshberg and Jones have already suggested an alternative explanation of the effect, *viz.*, the addition of alcohol to one of the carbonyl groups, in a manner known for aldehydes and ketones:



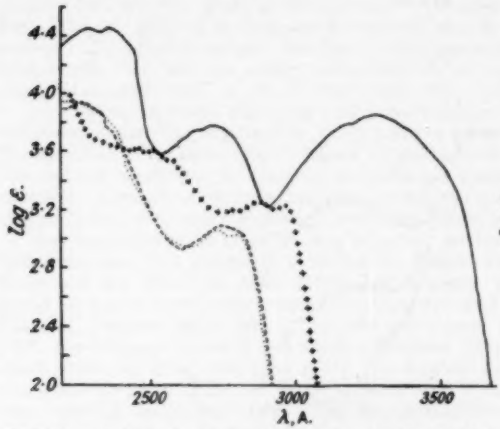




Indeed, there are certain reactions in which the carbonyl group of phthalic anhydride exhibits a reactivity resembling that of aldehydes, *e.g.*, condensation with acetic anhydride or phenylacetic acid (Gabriel, *Ber.*, 1881, **14**, 919; 1884, **17**, 2521; 1885, **18**, 3470; Michael and Gabriel, *Ber.*, 1877, **10**, 391; Gabriel and Michael, *ibid.*, p. 1552; 1878, **11**, 1007, 1017).

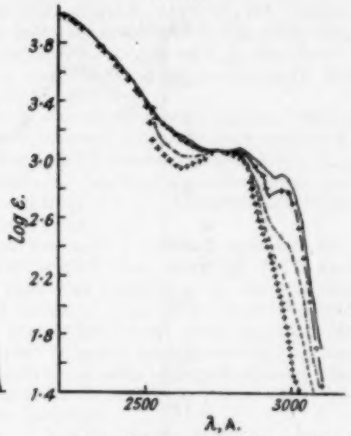
It appeared worth while to study the effect in a few simpler cases. Phthalic anhydride shows, immediately after dissolution, a different spectrum in dioxan and ethyl alcohol (Fig. 1); subsequently, the spectrum of the alcoholic solution slowly undergoes some very minor changes (Fig. 2) which do not cause any shift in the location or intensity of the absorption

FIG. 1.



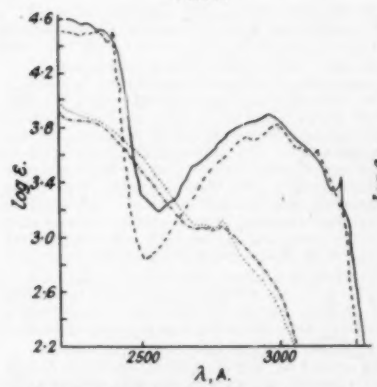
Phthalic anhydride in dioxan (+ + +) *and ethyl alcohol* (. . . .). *Ethyl phthalate in ethyl alcohol* (– – – –). *Hemipinic anhydride* (IV) *in isooctane* (———).

FIG. 2.



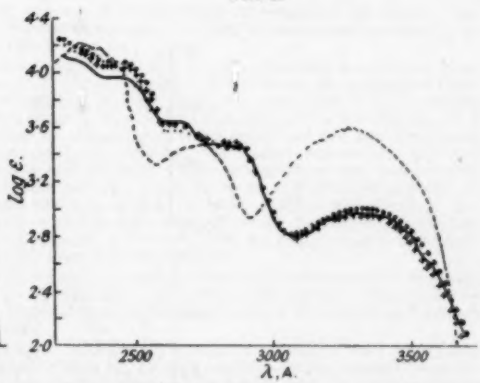
Alcoholic solution of phthalic anhydride: ——— *fresh*, — + — + *after* 80 *mins.*, — · — · *after* 3 *hrs.*, — — — *after* 5 *hrs.*, + + + *after* 24 *hrs.*

FIG. 3.



α-Methoxyphthalide (II) *in dioxan* (. . . .) *and ethyl alcohol* (— · — · —). *Naphthalide* (VII) *in isooctane* (———). *Methoxynaphthalide* (VIII) *in isooctane.*

FIG. 4.

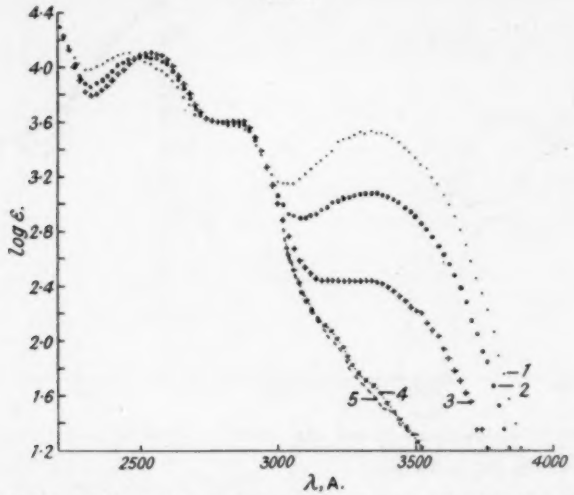


Metahemipinic anhydride (III) *in* isooctane (– – – –) *and ethyl alcohol* (——— *fresh*; • • • • *after* 2 *hrs.*; + + + + *after* 24 *hrs.*; . . . . *after* 20 *days*).

maximum at 2750 A. In view of the fact that Anderson and Kenyon (*loc. cit.*) have isolated only unchanged phthalic anhydride from its alcoholic solution after one hour (at room temperature), it may be assumed that phthalic anhydride forms a " hemiacetal " (I) of the above type which gradually isomerizes to the monoester. This assumption is supported by the observation that 3-methoxyphthalide (II) has—in both alcohol and dioxan—a spectrum which closely resembles that of phthalic anhydride in alcohol (Fig. 3). It is likely that the difference in

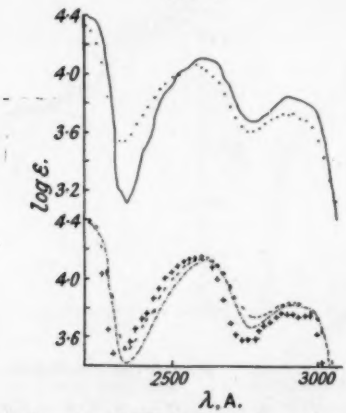
structure between (I) and (II), *viz.*, the absence of a hydroxyl group at the saturated α-carbon atom in (II), would not have a far-reaching influence on the spectrum. Further, any ester of phthalic acid, as the absorbing system is not very different from that of phthalic anhydride, should show approximately the same ultra-violet absorption curve. As Fig. 1 shows, for ethyl phthalate, this is, indeed, the case.

FIG. 5.



Hemipinic anhydride (IV) *in alcohol* : 1, *fresh*; 2, *after* 90 *mins.*; 3, *after* 4 *hrs.*; 4, *after* 24 *hrs.*; 5, *after* 71 *hrs.*

FIG. 6.



Upper part : 3 : 4-*dimethoxybenzoic acid* (VI) *in dioxan* (———) *and ethyl alcohol* (. . . .).
Lower part : *its methyl ester in dioxan* (— · — ·), isooctane (+ + + +), *and ethyl alcohol* (– – – –).

In the case also of metahemipinic (4 : 5-dimethoxyphthalic) anhydride (III), the fresh solution in alcohol shows a marked difference from that in *iso*octane. However, during twenty days, no further change takes place in the spectrum (Fig. 4). This could be interpreted to mean that the monoester is formed almost instantaneously and, indeed, working-up of an alcoholic solution after only a short time yields the ethyl hydrogen ester of m. p. 127° (Rossin, *Monatsh.*,

1891, **12**, 489). The nature of this product has also been established by titration (at 0°) and determination of the saponification number.

On the other hand, hemipinic anhydride (IV) shows the same behaviour as phthalic anhydride, only in a more pronounced manner. The initial difference between its solutions in isooctane and ethyl alcohol is greater (Fig. 1), and in the subsequent slow change in the spectrum of the alcoholic solution (Fig. 5) the maximum at 3280 A. disappears completely. It is not unlikely that the ester group of the product (V) (Wegscheider, *Monatsh.*, 1895, **16**, 141; Kahn, *Ber.*, 1903, **36**, 2533) is so completely hindered that it does not contribute to the absorbing system. The ester (V) should, therefore, have a spectrum similar to that of 3 : 4-dimethoxybenzoic acid (VI), and its methyl ester, and this is the case, as Fig. 6 shows (compare the spectrum of vanillic acid, Pearl, *J. Amer. Chem. Soc.*, 1948, **71**, 2331).

In order to complete Hirshberg and Jones's studies in the naphthalene-1 : 2-dicarboxylic anhydride series, the naphthalide (VII) and its methoxy-derivative (VIII) were prepared. The spectrum of the latter (Fig. 3) [which, of course, is substantially identical with that of (VII)] has definite similarity to that of an alcoholic solution of naphthalene-1 : 2-dicarboxylic anhydride, especially if one takes into account that (VII) is analogous to (*B*), whilst the anhydride may, at least partly, also add alcohol to form an adduct of type (*A*).

For the preparation of (VII), the following method was used: 2-methylnaphthalene-1-carboxylic acid was prepared according to Mayer and Sieglitz (*Ber.*, 1922, **55**, 1851) and Shoesmith and Rubli (*J.*, 1927, 3102), and its methyl ester was brominated in the 2-methyl group by means of *N*-bromosuccinimide (Newman and Kosak, *J. Org. Chem.*, 1949, **14**, 375; Buu-Hoï, *Annalen*, 1944, **556**, 1; Schmid and Karrer, *Helv. Chim. Acta*, 1946, **29**, 573). At 150°, the bromo-compound lost methyl bromide (Mayer, Schaefer, and Rosenbach, *Chem. Zentr.*, 1929, II, 3009) and gave (VII). As a model experiment with phthalide showed, the methylene group in (VII) can be brominated with *N*-bromosuccinimide; in the product, the bromine atom was replaced by methoxyl, on heating with methanol.

Experimental.

3-Methoxyphthalide (II).—Phthalide was brominated at 140°, according to Racine (*Annalen*, 1887, **239**, 79); the same 3-bromophthalide was obtained in excellent yield when phthalide (2·0 g.) was refluxed with *N*-bromosuccinimide (3·0 g.) in carbon tetrachloride (30 c.c.) for 2 hours and the filtered solution concentrated. From methylcyclohexane, leaflets, m. p. 81°, were obtained.

3-Bromophthalide (15 g.) was refluxed for 6 hours with five times its weight of methanol. The product which remained after removal of the solvent was purified by distillation *in vacuo* and had b. p. 149—151°/20 mm, m. p. 44° (yield, 9 g., 79%) (Racine, *loc. cit.*).

Methoxynaphthalide (*3-Methoxy-6 : 7-benzophthalide*) (VIII).—*2-Methylnaphthalene-1-carboxylic acid.* A solution of 1-bromo-2-methylnaphthalene (100 g.; b. p. 168—170°/20 mm.) in anhydrous ether (300 c.c.) was added during 15 minutes to magnesium turnings (13 g.) in ether (100 c.c.) containing methyl iodide (*ca.* 2 c.c.). A vigorous reaction set in. The mixture was refluxed for 8 hours (in a few runs the complex which separated was dissolved by the addition of benzene), and the solution poured on solid carbon dioxide (160 g.). When the gas evolution subsided, the product was decomposed with ice-water (350 g.) and concentrated hydrochloric acid (40 c.c.). The ethereal layer was washed with water and extracted with 10% sodium carbonate solution, until no more acid was precipitated on acidification. The combined sodium carbonate solutions were filtered and acidified with dilute hydrochloric acid. 2-Methylnaphthalene-1-carboxylic acid separated as an oil which crystallized on storage. Recrystallization from acetic acid gave white prisms, m. p. 126—127° (41 g., 36%). Some unchanged 1-bromo-2-methylnaphthalene could be recovered from the ethereal layer.

The acid chloride was prepared in quantitative yield, by refluxing the acid for 3 hours with an excess of thionyl chloride, as a yellow oil, b. p. 178—181°/27 mm. Refluxing with methanol then gave the methyl ester, b. p. 149—155°/6 mm., which separated as an oil and was washed with water and sodium carbonate solution and extracted with chloroform.

Methyl 2-bromomethylnaphthalene-1-carboxylate. The preceding ester (8 g.) was refluxed for 4 hours with *N*-bromosuccinimide (7·8 g.) in carbon tetrachloride (40 c.c.) in presence of some benzoyl peroxide. After cooling, the succinimide was filtered off and the filtrate evaporated to dryness, leaving a brown oil which could not be induced to crystallize. At 150°, it decomposed with evolution of methyl bromide and gave the *2-hydroxymethylnaphthalene-1-carboxylic lactone* (*naphthalide*) (VII). This crystallized on cooling. From glacial acetic acid (charcoal), it formed white leaflets, m. p. 157° (5 g.) (Found: C, 78·3; H, 4·2. $C_{12}H_8O_2$ requires C, 78·3; H, 4·3%).

The 3-bromonaphthalide. The naphthalide (VII) (1·8 g.) was refluxed for 4 hours with *N*-bromosuccinimide (2 g.) in carbon tetrachloride (20 c.c.). The succinimide was filtered off, the solvent evaporated, and the residual *bromo*-compound (2·7 g.) recrystallized from light petroleum–benzene as needles, m. p. 140° (Found: Br, 30·6. $C_{12}H_7O_2Br$ requires Br, 30·4%).

The 3-methoxynaphthalide (VIII). The bromo-lactone (0·5 g.) was refluxed for 3 hours in 10 c.c. of anhydrous methanol. After removal of the methanol, an oily residue of *methoxynaphthalide* remained, which crystallized on storage. From light petroleum–benzene it formed white needles, m. p. 79—80° (yield, quantitative) (Found: C, 72·8; H, 4·9. $C_{13}H_{10}O_2$ requires C, 72·9; H, 4·7%).

Phthalic, hemipinic, and metahemipinic anhydrides were commercial samples, which were recrystallized from benzene, xylene, and butyl acetate, respectively; they then had m. p. 127°, 169°, and 175°, respectively. Ethyl phthalate, purified by distillation, had b. p. 156°/10 mm. 3 : 4-Dimethoxybenzoic acid, prepared by oxidation of veratraldehyde with permanganate (Edwards, Perkin, and Stoyle, *J.*, 1925, **127**, 198) and crystallised from *iso*propanol, had m. p. 181°. Treatment with an excess of ethereal diazomethane gave methyl 3 : 4-dimethoxybenzoate (from methyl*cyclo*hexane), m. p. 62° (Tiemann, *Ber.*, 1875, **8**, 1123).

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230. *Reactions in Sunlight of Certain Diketones with Ethylenes and Aromatic Aldehydes. Photopolymerisation of 9-Anthraldehyde.*

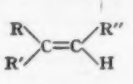
By AHMED MUSTAFA.

Phenanthraquinone reacts in sunlight with the unsaturated compounds (I*b*—III*c*, IV—V*b*) to give the photo-products (VII—IX*c*, X—XI*b*), respectively; similarly, retenequinone with (III*d*) and (VI) forms (XII) and (XIII), respectively, and the photo-product from *pp'*-dianisil and (I*a*) has the structure (XIV) (see Table I).

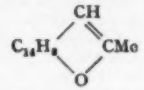
The photo-reaction between phenanthraquinone and 2-formylquinoline or 9-anthraldehyde to give (XV*a*) and (XV*b*), and that between retenequinone or chrysoquinone and 9-anthraldehyde, giving (XVI) and (XVII), respectively, are described (see Table II).

(*c*) A solution of 9-anthraldehyde in benzene, on exposure to sunlight, gives the dimer $(C_{15}H_{10}O)_2$.

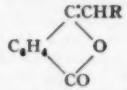
THE work on the action of certain unsaturated compounds on phenanthraquinone to form derivatives of phenanthro-1 : 4-dioxen (Schönberg and Mustafa, *Chem. Reviews*, 1947, **40**, 181; Mustafa and Islam, *J.*, 1949, S 81; Mustafa, *ibid.*, p. S 83) has now been extended (see Table I, reaction A). Phenanthraquinone has been allowed to react with the unsaturated compounds



(I*a*; R = R'' = Ph, R' = H.)
(I*b*; R = R' = CH_2Ph, R'' = Ph.)

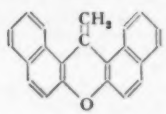


(II.) *

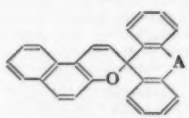


(III*a*; R = Me.)
(III*b*; R = Et.)
(III*c*; R = C_5H_{11}.)
(III*d*; R = Ph.)

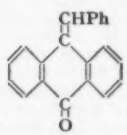
* Here and elsewhere, $C_{14}H_8$ = 9 : 10-phenanthrylene.



(IV.)

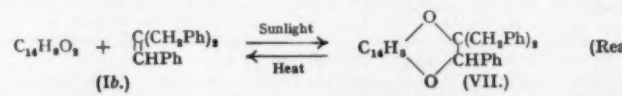


(V*a*; A = O.) (V*b*; A = S.)



(VI.)

(I*b*), (II), (III*a*, *b*, and *c*), (IV), and (V*a* and *b*); also retenequinone with (III*d*) and (VI); and *pp'*-dianisil with (I*a*). We believe that the products are in all cases cyclic diethers formed by addition across the double bond (for the products in each particular case see Tables I and III, and the formulæ and Reaction A). These constitutions are based on the facts that the products are colourless or almost colourless, in contrast to the deep colour of the original quinones, and

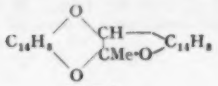


(I*b*.) (VII.) (Reaction A)

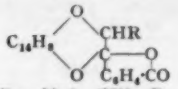
that heating decomposes the products into their generators, except that (III*b*) and (III*c*) were not obtained from (IX*b*) and (IX*c*), probably because of their thermolability.

The velocities of the reactions between olefins and *o*-quinones differ. In general, the velocity with which benzil and *pp'*-dianisil react is much less than that of phenanthraquinone, retenequinone, and chrysoquinone. Triketoindane (Schönberg, Mustafa, *et al.*, *J.*, 1948, 2126) reacts moderately rapidly.

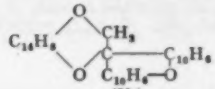
Recently, Mustafa (*loc. cit.*) described a number of photo-reactions between retenequinone and aromatic aldehydes. A similar reaction (Mustafa, *Nature*, 1950, **166**, 108) has been carried



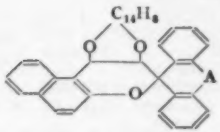
(VIII.)



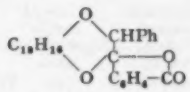
(IX*a*; R = Me.) (IX*b*; R = Et.)
(IX*c*; R = C_6H_{11}.)



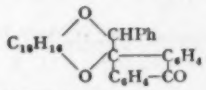
(X.)



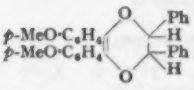
(XI*a*; A = O.)
(XI*b*; A = S.)



(XII.) •



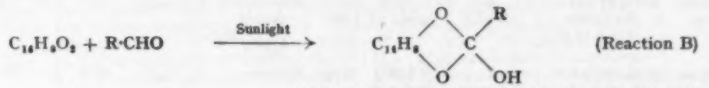
(XIII.) •



(XIV.)

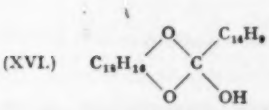
• In these formulæ, $C_{18}H_{16}$ = 1-methyl-7-*iso*propylphenanthrene residue.

out with 2-formylquinoline or 9-anthraldehyde and phenanthraquinone (see Reaction B), and with 9-anthraldehyde and retenequinone or chrysoquinone. The addition products (Table II) were the hydroxymethylene ethers (orthocarboxylates) (XV*a* and *b*), (XVI), and (XVII).

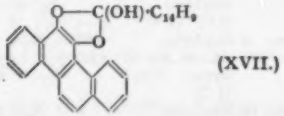


(Reaction B)

(XV*a*; R = 2-quinolyl.) (XV*b*; R = 9-anthryl.)



(XVI.)



(XVII.)

When a benzene solution of 9-anthraldehyde was exposed to sunlight (cf. Mustafa, *loc. cit.*, and the photopolymerisation of benzaldehyde in sunlight, Ciamician and Silber, *Ber.*, 1903, **36**, 1575), an almost colourless photo-dimer $(C_{15}H_{10}O)_2$ was formed. Its constitution is based on (i) its lack of colour, (ii) its regeneration of 9-anthraldehyde when heated at 270°, and (iii) its molecular weight.

Experimental.

All reactions were in solution unless otherwise stated. The benzene (30 c.c. for each experiment) was free from toluene (cf. Mustafa, *loc. cit.*) and thiophen and had been dried over sodium. The reaction mixtures were placed in a 25-cm. Schlenk tube (Schlenk and Thal, *Ber.*, 1913, **46**, 2655; Houben, "Die Methoden der Organischen Chemie," 2nd edn., Vol. IV, 960) of Pyrex glass, the air was displaced by dry carbon dioxide, and the tube sealed. Control experiments in the dark, but otherwise under identical conditions, showed no reaction (cf. Schönberg and Latif, *J. Amer. Chem. Soc.*, 1950, **72**, 4828).

Thermal Decomposition of the Addition Products (VII—XIV).—The addition products, when heated at 270° (bath-temp.) [except (XI*a*) which was at 300° (bath-temp.)] in a stream of dry carbon dioxide for ½ hour, decomposed into their generators which were separated as follows: (*a*) In the case of (VII), (VIII), (IX*a*), (X), and (XII—XIV), the contents of the tube were treated with hot ligroin (b. p. 70—80°); the part which went into solution proved to be the corresponding ethylene, and the insoluble part, after crystallisation from boiling ethyl alcohol, proved to be the corresponding 1 : 2-diketone. (*b*) With

(XI*a*) and (XI*b*), the contents of the tube were treated with hot ethyl alcohol; the soluble part was phenanthraquinone and the insoluble part, after crystallisation from benzene, proved to be the ethylene derivative.

The thermal decomposition products were identified in all the cases by m. p. and mixed m. p. determinations and colour reaction with sulphuric acid.

Photopolymerisation of 9-Anthraldehyde.—A solution of 9-anthraldehyde (Fieser and Hartwell, *loc. cit.*) (1 g.) in benzene (25 c.c.) was exposed to sunlight for 4 days (June). The crystals that separated were filtered off, washed with light petroleum (b. p. 30—50°), and crystallised from benzene, forming almost colourless crystals, m. p. 250° (decomp.; yellow melt) [Found: C, 87·6; H, 4·8%; *M* (micro-Rast), 402. $C_{30}H_{20}O_2$ requires C, 87·4; H, 4·8%; *M*, 412]. The photo-*dimer* gave a deep red colour

TABLE I.

(Reaction A).

(For names of products, see Table III.)

Diketone, and wt. (g.).	Ethylenic compd., and wt. (g.).	Time of irradiation, days.	Number, m. p., and colour with H_2SO_4 of addition product.	Recrystn. solvent.	Formula of product.	Analysis of product. Found, %. C.	H.	Reqd., %. C.	H.
Phenanthraquinone (1·0)	2-Benzyl-1 : 3-diphenylpropene (I*b*) [a] (1·4)	40 (Jan.–Feb.)	VII, 220°, olive-green	(See footnotes 1, 2)	$C_{34}H_{28}O_2$	87·4	5·6	87·4	5·7
Phenanthraquinone (1·3)	5-Methylphenanthro-(9′ : 10′-1 : 2)-furan (II) [b] (1·4)	60 (Mar.–April)	VIII, >260°, olive-green	Xylene [a]	$C_{31}H_{20}O_3$	84·3	4·2	84·5	4·5 †
Phenanthraquinone (1·0)	Ethylidenephthalide (III*a*) (0·8)	4 (Mar.)	IX*a*, 240°, olive-green at 100°	Xylene [2]	$C_{24}H_{16}O_4$	78·2	4·2	78·3	4·3
Phenanthraquinone (1·0)	*n*-Propylidenephthalide (III*b*) (0·8)	7 (Mar.)	IX*b*, 210°, olive-green at 100°	Benzene [2]	$C_{25}H_{18}O_4$	78·6	4·5	78·5	4·7
Phenanthraquinone (1·0)	*n*-Hexylidenephthalide (III*c*) (1·0)	4 (Mar.)	IX*c*, 240°, olive-green at 100°	Benzene–petrol (b. p. 30—50°) [2]	$C_{28}H_{24}O_4$	78·9	5·6	79·3	5·6
Phenanthraquinone (1·0)	9-Methylene-1 : 2-7 : 8-dibenzoxanthen (IV) [c] (1·4)	7 (June)	X, 226°, deep violet	Xylene	$C_{34}H_{22}O_3$ [1]	85·8	4·2	86·1	4·4
Phenanthraquinone (1·0)	β-Naphthoxanthos*piro*pyran (V*a*) [d] (1·7)	25 (July)	XI*a*, >250°, brown changing to violet	Benzene	$C_{39}H_{24}O_4$	83·9	4·3	84·1	4·3 ‡
Phenanthraquinone (1·0)	β-Naphthothiaxantho*spiro*pyran (V*b*) [e] (1·8)	7 (Mar.)	XI*b*, 254° olive-green at 100°	Xylene [2]	$C_{39}H_{24}O_3S$	81·6	4·2	81·8	4·2 §
Retenequinone (1·0)	Benzylidenephthalide (III*d*) [f] (0·8)	20 (May)	XII, 212°, olive-green at 100°	Benzene [2]	$C_{32}H_{24}O_4$	81·1	4·9	81·5	5·3
Retenequinone (1·0)	9-Benzylideneanthrone (VI) [g] (1·1)	50 (May–June)	XIII, 230°, red-violet	Benzene [2]	$C_{29}H_{20}O_3$	85·5	5·3	85·7	5·5
pp′-Dianisil (1·0)	Stilbene (I*a*) (0·7)	*ca.* 90 (May–July)	(XIV) 258°, orange-yellow	Xylene	$C_{30}H_{24}O_4$	79·8	5·6	80·0	5·8

References: [a] Orechov and Grinberg, *J. Russ. Phys. Chem. Soc.*, 1916, **48**, 1713; [b] Japp and Klingemann, *Ber.*, 1888, **21**, 2932; [c] Wizinger and Al-Atter, *Helv. Chim. Acta*, 1947, **30**, 189; [d] Irving, *J.*, 1929, 1093; [e] Mustafa, *J.*, 1949, 2295; [f] Gabriel, *Org. Synth.*, Vol. XIII, 10; [g] Cook, *J.*, 1926, 2160.

[1] The benzene solution was evaporated, and the residual oil solidified when washed with cold light petroleum (b. p. 40—60°) and with absolute ethyl alcohol and crystallised from benzene–light petroleum (b.p. 30—50°). [2] Yield almost quantitative.

[a] After being washed with hot ethanol. † *M* (micro-Rast), 428 (required, 440). ‡ *M* (micro-Rast), 540 (required, 556). § S, 5·1 (required, S, 5·6%).

TABLE II.

(Reaction B).

(For names of products, see Table III.)

Quinone, and wt. (g.).	Aldehyde, and wt. (g.).	Time of irradiation, days.	Number, m. p., and colour with H_2SO_4 of addition product.	Recrystn. solvent.	Formula of product.	Analysis of product. Found, %. C.	H.	Reqd., %. C.	H.
Phenanthraquinone (1·0)	2-Formylquinoline [a] (0·7)	3 (Dec.)	(XV*a*), 224°, olive-green	Xylene [1] *	$C_{24}H_{15}O_2N$	78·7	3·9	78·9	4·1 ‡
Phenanthraquinone (1·0)	9-Anthraldehyde [b] (1·0)	20 (Mar.)	(XV*b*), 228°, olive-green	Xylene [1]	$C_{29}H_{18}O_2$	84·1	4·3	84·1	4·3 §
Retenequinone (1·0)	9-Anthraldehyde [b] (0·8)	20 (Mar.)	(XVI), 187°, brownish-green	Benzene *	$C_{32}H_{24}O_2$	84·1	5·3	84·3	5·5
Chrysoquinone (1·0)	9-Anthraldehyde [b] (0·8)	20 (Mar.)	(XVII), 190°, violet-blue	Xylene [1] †	$C_{32}H_{22}O_2$	85·0	4·2	85·3	4·3

References: [a] Kaplan, *J. Amer. Chem. Soc.*, 1941, **63**, 2655; [b] Fieser and Hartwell, *Org. Synth.*, Vol. 20, p. 11.

[1] Yield almost quantitative.

* After being washed with hot ethanol. † After being washed with boiling acetone. ‡ Found: N, 3·5. Reqd.: N, 3·8%. § *M* (micro-Rast), 401 (required, 414).

TABLE III.

Formal names of products given in Tables I *and* II.

Number.	Name.
VII	5 : 5-Dibenzyl-6-phenylphenanthro(9′ : 10′-2 : 3)dioxen.
VIII	4 : 5-Dihydro-5-methyl-4 : 5-phenanthrylenedioxyphenanthro(9′ : 10′-2 : 3)furan.
IX*a*	6-Methylphenanthro(9′ : 10′-2 : 3)dioxen-5-*spiro*-3″-phthalide.
IX*b*	6-Ethylphenanthro(9′ : 10′-2 : 3)dioxen-5-*spiro*-3″-phthalide.
IX*c*	6-*n*-Pentylphenanthro(9′ : 10′-2 : 3)dioxen-5-*spiro*-3″-phthalide.
X	Phenanthro(9′ : 10′-2 : 3)dioxen-5-*spiro*-9″-(1″ : 2″-7″ : 8″-dibenzoxanthen).
XI*a*	4 : 5-Phenanthrylenedioxynaphtho(2′ : 1′-2 : 3)pyran-6-*spiro*-9″-xanthen.
XI*b*	4 : 5-Phenanthrylenedioxynaphtho(2′ : 1′-2 : 3)pyran-6-*spiro*-9″-thioxanthen.
XII	1′-Methyl-6-phenyl-7′-*iso*propylphenanthro(9′ : 10′-2 : 3)dioxen-5-*spiro*-3″-phthalide.
XIII	1′-Methyl-6-phenyl-7′-*iso*propylphenanthro(9′ : 10′-2 : 3)dioxen-5-*spiro*-9″-anthrone.
XIV	2 : 3-Di-*p*-methoxyphenyl-5 : 6-diphenyl-Δ^3-dioxen.
XV*a*	2-Hydroxy-2-2″-quinolylphenanthro(9′ : 10′-4 : 5)dioxole.
XV*b*	2-9″-Anthryl-2-hydroxyphenanthro(9′ : 10′-4 : 5)dioxole.
XVI	2-9″-Anthryl-2-hydroxy-1′-methyl-7′-*iso*propylphenanthro(9′ : 10′-4 : 5)dioxole.
XVII	2-9″-Anthryl-2-hydroxychryseno(1′ : 2′-4 : 5)dioxole.

with sulphuric acid, and was soluble in hot benzene or xylene and difficultly soluble in ethyl alcohol. When heated at 270° (bath-temp.), it afforded 9-anthraldehyde (m. p. and mixed m. p. and colour reaction with sulphuric acid).

The author is indebted to Dr. D. T. Mowry (Central Research Laboratories of the Monsanto Chemical Co., Dayton, Ohio) for the gift of ethylidene-, *n*-propylidene-, and *n*-hexylidene-phthalides.

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[*Received, January 4th*, 1951.]

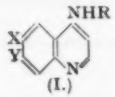
231. *Synthetic Antimalarials. Part XLVI. Some 4-Dialkylaminoalkylaminoquinoline Derivatives.*

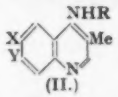
By Justus K. Landquist.

The 4-3′-diethylaminopropylamino-derivatives of quinoline, 2- and 3-methylquinoline, and 2 : 3-dimethylquinoline, and the corresponding 6-methoxy- and 7-chloro-compounds have been made. Their absorption spectra and antimalarial activities are discussed. The orientation of the 7-chloro-compounds was established by synthesis. Preparation of miscellaneous 4-dialkylaminoalkylaminoquinoline derivatives from 4-chloroquinolines, 2 : 4-dihydroxyquinolines, and quinoline-4-sulphonic acids is described. Formation of acylanthranilic acids in the Camps 4-hydroxyquinoline synthesis, and of a 4-ethoxyquinoline derivative in the Conrad–Limpach reaction, is recorded.

Concurrently with the investigations described in other papers of this series, a limited study of certain 4-dialkylaminoalkylaminoquinolines was made. Conflicting reports about the antimalarial activity of compounds of this type had appeared in the literature. Thus, Holcomb and Hamilton (*J. Amer. Chem. Soc.*, 1942, **64**, 1309) stated that 4-3′-diethylaminopropylamino-6-methoxyquinaldine is active in avian malaria although Kermack and Smith (*J.*, 1931, 3096) and Magidson and Rubtsov (*J. Gen. Chem., U.S.S.R.*, 1937, **7**, 1896) had reported that compounds of this type are inactive. Schönhöfer (*Z. physiol. Chem.*, 1942, **274**, 1) stated that 4-(4-diethylamino-1-methylbutylamino)-6-methoxyquinoline is active and in B.P. Appl. 27,673/38 and its foreign equivalents (G.P. 683,692; U.S.P. 2,233,970, etc.) I.G. Farbenind. claimed high antimalarial activity for 4-aminoalkylaminoquinolines bearing at least a further substituent in the 7-position, but stated that the 2-position should be unsubstituted. It seemed likely that these discrepancies were due to differences in susceptibility to a given drug between different species of plasmodia either in the same or in different hosts (cf. Curd, *Ann. Trop. Med. Parasitol.*, 1943, **37**, 115). The importance of species susceptibility in relation to the search for new antimalarial drugs has been discussed by Davey (*ibid.*, 1946, **40**, 52) and the 4-dialkylaminoalkylaminoquinolines appeared to afford a suitable class of compounds with which to study this problem.

The synthesis of representative compounds of this class was undertaken to determine whether German work subsequent to the discovery of mepacrine had disclosed antimalarials of greater potency, to examine these drugs against the species of plasmodia used in these laboratories, and to provide a basis for comparison with our own novel types. When the work was projected in 1942 no proof had been offered of the structure of the 7-chloro-4-dialkylaminoalkylaminoquinolines, so unambiguous syntheses were devised. Since the completion of this work details of the preparation and clinical testing of 7-chloro-4-(4-diethylamino-1-methylbutylamino)-quinoline (" Chloroquine ") and its 3-methyl derivative (" Sontochin ") have been published (Wiselogle, " Survey of Antimalarial Drugs, 1941—1945," Edwards, Ann Arbor, 1946; C.I.O.S. Reports XXIII-12, XXV-54; Drake *et al.*, *J. Amer. Chem. Soc.*, 1946, **68**, 1214, etc.).


(I.)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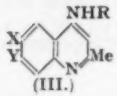
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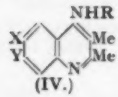
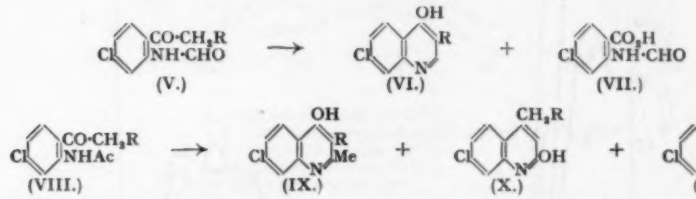
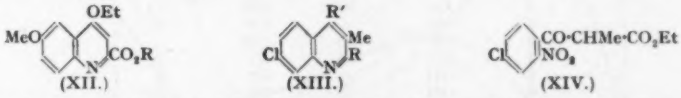

(IV.)

Apart from " Chloroquine " which was not then available from other sources, the substances synthesised fell into three series of four compounds (I—IV), where R = $Et_2N\cdot[CH_2]_3\cdot$ and (*a*) X = Y = H, (*b*) X = MeO, Y = H, and (*c*) X = H, Y = Cl, representing successive stages of simplification of the " Acrichin " molecule. The diethylaminopropyl side chain was chosen for convenience in synthesis; it gives high activity in known types of antimalarials, *e.g.*, " Plasmocide," " Acrichin," " Brachysan." A few further variations were examined. With the publication of the original German work (Andersag, *Ber.*, 1948, **81**, 499) and of numerous papers from American laboratories much of the preparative work has now been described, but a number of features of this investigation are novel.

4-Hydroxy-3-methylquinoline was made by heating 2-formamidopropiophenone with aqueous-alcoholic sodium hydroxide (cf. Camps, *Ber.*, 1899, **32**, 3228; 1901, **34**, 2703; Wohnlich, *Arch. Pharm.*, 1913, **251**, 526). Cyclisation of 4-chloro-2-formamido-acetophenone (V; R = H) and -propiophenone (V; R = Me) gave 7-chloro-4-hydroxyquinoline (VI; R = H) and its 3-methyl derivative, together with 4-chloro-*N*-formylanthranilic acid (VII). From 2-acetamido-4-chloroacetophenone (VIII; R = H) the Camps ring-closure gave 7-chloro-4-hydroxyquinaldine (IX; R = H), 7-chloro-2-hydroxylepidine (X; R = H), and *N*-acetyl-4-chloroanthranilic acid (XI), and similarly 2-acetamido-4-chloropropiophenone (VIII; R = Me) gave 7-chloro-4-hydroxy-2 : 3-dimethylquinoline (IX; R = Me), 7-chloro-4-ethyl-2-hydroxyquinoline (X; R = Me), and (XI). The formation of *N*-acylanthranilic acids in the Camps reaction has not hitherto been reported. The identity of the compounds (IX and X; R = H or Me) was established by comparison of their absorption spectra with those of known 2- and 4-hydroxyquinolines, and by syntheses by alternative routes. 7-Chloro-2-hydroxylepidine (X; R = H) is obtained by ring-closure of acetoaceto-*m*-chloroanilide with sulphuric acid (C.I.B.A., B.P. 351,605). Condensation of *m*-chloroaniline with acetoacetic ester and with α-methylacetoacetic ester by the Conrad–Limpach method gave mixtures of 5- and 7-chloroquinoline derivatives from which (IX; R = H and Me) were isolated (cf. Spivey and Curd, *J.*, 1949, 2656).



The yields of 4-hydroxyquinoline derivatives from the Camps reaction were poor, and larger quantities were made by condensation of arylamines with ethyl ethoxalylacetate, α-ethoxalylpropionate, or ethoxymethylenemalonate (Andersag, *loc. cit.*; Gould and Jacobs, *J. Amer. Chem. Soc.*, 1939, **61**, 2890; Surrey and Hammer, *ibid.*, 1946, **68**, 113; Steck, Hallock, and Holland, *ibid.*, pp. 129, 380; Price and Roberts, *ibid.*, p. 1204, etc.). In the preparation of ethyl 4-hydroxy-6-methoxyquinoline-2-carboxylate from *p*-anisidine and ethyl ethoxalylacetate the formation of a small amount of ethyl 4-ethoxy-6-methoxyquinoline-2-carboxylate (XII; R = Et) was observed. This compound separated from the mother-liquors from the cyclisation on long storage. Possibly this side reaction, the elimination of water instead of ethanol, occurs in other cases but the 4-ethoxyquinoline derivatives escape detection because of their greater



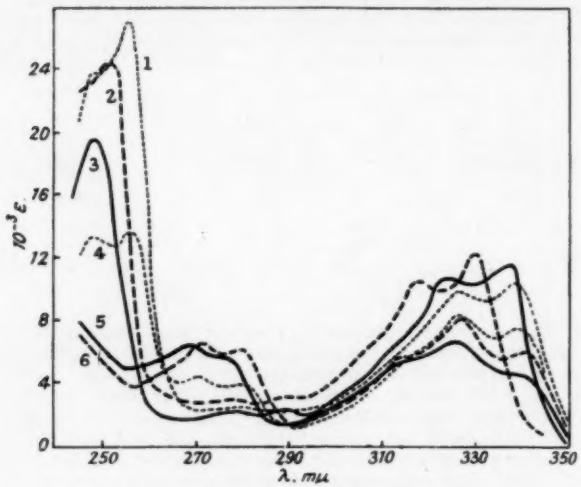
solubility in the reaction mixture. 4-Ethoxy-6-methoxyquinoline-2-carboxylic acid (XII; R = H) was decarboxylated above its m. p., giving 4-ethoxy-6-methoxyquinoline, but its hydrochloride under the same conditions was converted into 4-hydroxy-6-methoxyquinoline. As an alternative to ethyl ethoxalylacetate, ethyl acetylenedicarboxylate was condensed with *p*-anisidine to give ethyl 4-hydroxy-6-methoxyquinoline-2-carboxylate, but this route offered no advantage.

The preparation of 4-dialkylaminoalkylaminoquinolines from 2 : 4-dihydroxyquinolines by condensation with dialkylaminoalkylamines, conversion into 2-chloro-4-dialkylaminoalkylaminoquinolines, and dehalogenation by catalytic reduction (Part XVII, Curd, Raison, and Rose, *J.*, 1947, 899) was investigated further, and 4-3′-piperidinopropylaminoquinoline (I; X = Y = H, R = ·$[CH_2]_3$·N < $[CH_2]_5$), 4-3′-diethylaminopropylamino- and 4-(4-diethylamino-1-methylbutylamino)-3-methylquinoline (II; X = Y = H, R = ·$[CH_2]_3$·NEt_2 and ·CHMe·$[CH_2]_3$·NEt_2 respectively), and 4-3′-diethylaminopropylamino-7 : 8-benzoquinoline were made by this method. Attempts to prepare the 7-chloro-derivatives by selective reduction of 2 : 7-dichloro-4-3′-diethylaminopropylaminoquinoline (Part XVII) and 2 : 7-dichloro-4-3′-diethylaminopropylamino-3-methylquinoline (XIII; R = Cl, R′ = NH·$[CH_2]_3$·NEt_2) were

unsuccessful, the only identifiable products after absorption of the required amount of hydrogen being the halogen-free 4-3′-diethylaminopropylaminoquinoline (or its 3-methyl derivative) and unchanged dichloro-compound which were separated by crystallisation of their 3 : 5-dinitrobenzoates. 7-Chloro-2 : 4-dihydroxy-3-methylquinoline (XIII; R = R′ = OH) was obtained by condensing *m*-chloroaniline with ethyl methylmalonate (cf. Baumgarten and Kärgel, *Ber.*, 1927, **60**, 832) and was characterised by conversion into 2 : 4 : 7-trichloro-3-methylquinoline (XIII; R = R′ = Cl). The orientation of these compounds was established by their preparation from ethyl α-(4-chloro-2-nitrobenzoyl)propionate (XIV) by reduction and ring closure. Gentle hydrolysis of 2 : 4 : 7-trichloro-3-methylquinoline (cf. Rowlett and Lutz, *J. Amer. Chem. Soc.*, 1946, **68**, 1288) gave 4 : 7-dichloro-2-hydroxy-3-methylquinoline (XIII R = OH, R′ = Cl).

FIG. 1.

Absorption spectra of quinoline derivatives in chloroform.



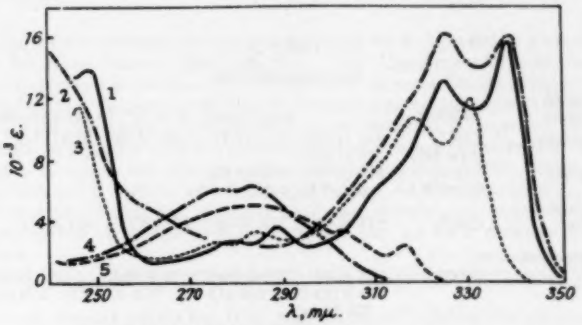
Substituent at position :

Curve no.	2.	3.	4.	7.
1	Me	Me	OH	Cl
2	Me	—	OH	Cl
3	Me	Me	OH	—
4	OH	—	Et	Cl
5	OH	—	Et	—
6	OH	—	Me	Cl

In general, the 4-dialkylaminoalkylaminoquinolines were prepared by heating the corresponding 4-chloroquinolines and dialkylaminoalkylamines at 180°. Condensation of quinoline-4-sulphonic acids with dialkylaminoalkylamines is a useful alternative (I.G. Farbenind., B.P. 437,317; Swiss P. 212,594; Rubtsov *et al.*, *J. Gen. Chem. U.S.S.R.*, 1946, **16**, 215, 1873; Walker, *J.*, 1947, 1552). 7-Chloroquinoline-4-sulphonic acid, prepared from 4 : 7-dichloroquinoline and sodium hydrogen sulphite (Norton, Benson, Seibert, and Bergstrom, *J. Amer. Chem. Soc.*, 1946, **68**, 1330), reacted very cleanly with 3-diethylaminopropylamine or 4-diethylamino-1-methylbutylamine in aqueous solution at 140—150°, giving (I; X = H, Y = Cl, R = $[CH_2]_3{\cdot}NEt_2$ or $CHMe{\cdot}[CH_2]_3{\cdot}NEt_2$). In B.P. 437,317 (I.G. Farbenind.) it was stated that quinoline-2 : 4-disulphonic acid is obtained from 2 : 4-dichloroquinoline and sodium sulphite, but under conditions comparable with the preparation of quinoline-4-sulphonic acid (Besthorn and Geisselbrecht, *Ber.*, 1920, **53**, 1017) the reaction was very sluggish and the product was 2-hydroxyquinoline-4-sulphonic acid. Reaction of this compound with aqueous 3-piperidinopropylamine at 140—150° gave 2-hydroxy-4-3′-piperidinopropylaminoquinoline which was also prepared from 2 : 4-dihydroxyquinoline and 3-piperidinopropylamine at 180°.

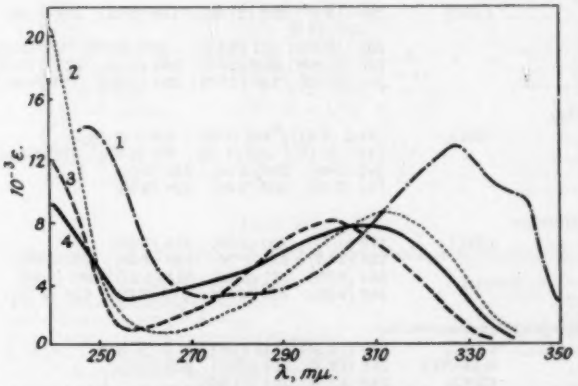
Reaction of (XIII; R = R′ = Cl) with sodium hydrogen sulphite was even more sluggish, the product being 7-chloro-2-hydroxy-3-methylquinoline-4-sulphonic acid (XIII; R = OH, R′ = SO_3H). In view of the instability of quinoline-2-sulphonic acid (Besthorn and Geisselbrecht, *loc. cit.*) the failure to obtain quinoline-2 : 4-disulphonic acids in these reactions is not surprising. Reaction of 2 : 4-dichloroquinoline with 4-diethylamino-1-methylbutylamine gave 2 : 4-bis-(4-diethylamino-1-methylbutylamino)quinoline.

FIG. 2.



1, 1-*Methyl-4-quinolone in* $CHCl_3$.
2, 4-3′-*Diethylaminopropylaminoquinoline in* 0·1N-HCl.
3, 4-*Hydroxyquinoline in* $CHCl_3$.
4, 4-*Methoxyquinoline in* $CHCl_3$.
5, 4-*Chloroquinoline in* $CHCl_3$.

FIG. 3.



1, 4-3′-*Diethylaminopropylaminoquinoline in* $CHCl_3$.
2, 4-*Hydroxyquinoline in* 0·1N-NaOH.
3, 4-*Methoxyquinoline in* 0·1N-HCl.
4, 1-*Methyl-4-quinolone in* 0·1N-HCl.

The ultra-violet absorption spectra of the 2- and 4-hydroxyquinolines produced by the Camps reaction were determined in order to identify the compounds. Both types have broadly similar spectra with three main regions of absorption at 230—250, 270—280, and 310—350 mμ., but the two series are sharply differentiated by the relative intensities of these bands. In the 2-hydroxyquinolines the middle bands are more intense than in the 4-hydroxy-compounds, and the long-wave-length band approximates to a triplet with the greatest absorption in the middle (Fig. 1). The spectrometric measurements were later extended to a number of 4-chloro-,

4-hydroxy-, and 4-3′-diethylaminopropylamino-quinolines in the hope of discovering some relation between molecular polarisation and antimalarial activity. Potentiometric and spectrometric studies of certain of these compounds have already been described by Gage (Part XLI, *J.*, 1949, 1458), and similar investigations have been made by Irvin and Irvin (*J. Amer. Chem. Soc.*, 1947, **69**, 1091), Steck and Ewing (*ibid.*, 1946, **68**, 2181; 1948, **70**, 3397), and Steck, Ewing, and Nachod (*ibid.*, 1948, **70**, 3410, 3954; 1949, **71**, 238, 2334). The last authors concluded that " little, if any, clear interrelation may be found between absorption spectra here determined and antimalarial activity," and the present studies have been no more

TABLE I.

Spectroscopic data.

Parent compound and substituent.	Solvent.	$\lambda_{max.}$ (mμ.); ε × 10^{-3} in parentheses.
1-Methyl-4-quinolone ...	$CHCl_3$	249 (13·9); 279 (2·76); 289 (3·88); 325 (13·2); 339 (15·8).
	0·1N-HCl	310 (7·61).
4-Methoxyquinoline ...	$CHCl_3$	277 (6·16); 283 (6·24).
	0·1N-HCl	~296 (7·60); 301 (8·02).
7-Chloro-2-hydroxy-4-methylquinoline	$CHCl_3$	271 (6·42); 279 (6·02); 327 (8·28); 341 (6·01).
4-Ethyl-2-hydroxyquinoline.		
Unsubstituted	$CHCl_3$	268 (6·35); 275·5 (5·61); 326 (6·68); ~340 (4·60).
7-Chloro	,,	248·5 (13·35); 256 (13·55); 270·5 (4·27); 279 (3·97); 326 (8·35); 339 (7·44).
4-Hydroxyquinoline.		
Unsubstituted	0·1N-NaOH	312 (8·60).
	$CHCl_3$	246 (11·6); 276 (2·71); 285 (3·43); 318 (10·75); 331 (12·1).
2-Methyl	,,	247 (13·75); 273 (1·96); 285 (2·70); 317 (10·7); 329 (11·5).
3-Methyl	,,	248 (17·15); 278 (2·52); 287 (3·20); 325 (10·95); 338 (12·6).
2 : 3-Dimethyl	,,	248 (19·65); 277 (2·13); 288 (2·22); 324 (10·7); 337 (11·7).
7-Chloro-4-hydroxyquinoline.		
Unsubstituted	$CHCl_3$	246 (19·2); 253 (21·35); 278 (2·02); 290 (2·34); 320 (10·3); 333 (12·0).
2-Methyl	,,	252 (24·25); 277 (2·84); ~290 (3·00); 318 (10·65); 330 (12·4).
3-Methyl	,,	248 (22·85); 255 (26·7); 280 (1·55); 327·5 (9·35); 340 (10·3).
2 : 3-Dimethyl	,,	249 (23·85); 256 (27·2); 281 (2·34); 326 (9·90); 339 (10·55).
4-Chloroquinoline.		
Unsubstituted	$CHCl_3$	284·5 (5·04); 303 (3·37); 316·5 (2·53).
2-Methyl	,,	245·5 (5·15); 282 (4·52); 307 (3·55); 320 (3·63).
3-Methyl	,,	282 (3·66); 306 (2·54); 320 (2·61).
2 : 3-Dimethyl	,,	282 (3·50); 306 (3·08); 320 (3·83).
4 : 7-Dichloroquinoline.		
Unsubstituted	$CHCl_3$	279 (4·73); 310 (2·86); 324 (3·30).
2-Methyl	,,	243 (4·07); 278 (4·76); 310 (3·68); 324 (4·68).
3-Methyl	,,	244 (3·29); 277 (5·25); 314 (3·32); 327 (3·84).
2 : 3-Dimethyl	,,	243 (4·30); 276 (4·70); 312 (3·63); 326 (4·74).
4-3′-Diethylaminopropylaminoquinoline.		
Unsubstituted	$CHCl_3$	248 (14·15); 328 (12·85); ~ *ca.* 340.
	0·1N-HCl	232 (19·3); 326 (16·1); 339 (16·0).
2-Methyl	$CHCl_3$	248 (17·5); 321 (11·45).
	0·1N-HCl	233 (21·3); 323 (15·0); 333 (14·2).
3-Methyl	$CHCl_3$	247·5 (19·4); 328 (8·55).
	0·1N-HCl	243 (26·1); 336 (15·35); 348 (15·3).
2 : 3-Dimethyl	$CHCl_3$	247 (20·2); 318 (7·47).
	0·1N-HCl	244 (30·3); 333·5 (14·5); 342 (14·3).
7-Chloro-4-3′-diethylaminopropylaminoquinoline.		
Unsubstituted	0·1N-HCl	~249 (16·4); 255 (17·0); 328 (18·0); 341 (18·7).
2-Methyl	$CHCl_3$	253·5 (18·7); 326 (12·3); ~ *ca.* 335.
	0·1N-HCl	246·5 (19·35); 324 (15·7); 335 (15·75).
3-Methyl	$CHCl_3$	257 (22·25); 335 (7·88).
	0·1N-HCl	253·5 (17·0); 337 (10·5); 350 (10·65).
2 : 3-Dimethyl	$CHCl_3$	253 (21·8); 323 (6·11).
	0·1N-HCl	255 (33·15); 335 (14·0); 346 (13·85).

successful. Gage (*loc. cit.*) suggested a possible relation between antimalarial activity of 4-aminoquinoline derivatives and the difference between the extinction coefficients of the two peaks in the range 325—350 mμ., but this has not been confirmed.

(XV.) (XVI.)

Because of its high basic strength the 4-aminoquinoline ion is regarded as a resonance hybrid (XV) (Albert and Goldacre, *Nature*, **1944**, **153**, 467). The resemblance between the absorption spectra of 4-aminoquinoline derivatives in dilute acid and those of 1-methyl-4-quinolone (XVI) and " 4-hydroxyquinoline " (4-quinolone) (Fig. 2) in which similar resonance is possible supports this view. When such resonance is prevented, *e.g.*, by addition of a proton to 1-methyl-4-quinolone or removal of a proton from 4-hydroxyquinoline, the two characteristic maxima in the 310—350 mμ. region disappear and there is more diffuse absorption at 300—320 mμ. resembling that of 4-aminoquinoline derivatives as free bases (Fig. 3). 4-Chloroquinoline derivatives and quinoline itself (Steck and Ewing, *loc. cit.*) have two sharp maxima in the region 300—320 mμ. which may be indicative of similar resonance forms, but no such maxima are shown by 4-methoxyquinoline.

The spectroscopic data, which were determined with a Beckman quartz spectrophotometer, are given in Table I.

The results of tests carried out by Dr. D. G. Davey (*loc. cit.*) against the blood-invasive form of *P. gallinaceum* in chicks are indicated in Tables II and III. In all three series substitution in

TABLE II.

Antimalarial activity of 4-3′-diethylaminopropylaminoquinolines.

Ref. no.	Substituents.	Formula.	Approx. M.E.D., mg./kg.
5271	—	I; X = Y = H	20
5284	3-Me	II; X = Y = H	40
4628	2-Me	III; X = Y = H	80
5372	2 : 3-Me_2	IV; X = Y = H	>80
5293	6-MeO	I; X = OMe, Y = H	20
5120	6-MeO-3-Me	II; X = OMe, Y = H	80
4935	6-MeO-2-Me	III; X = OMe, Y = H	>40
5068	6-MeO-2 : 3-Me_2	IV; X = OMe, Y = H	>160
5371	7-Cl	I; X = H, Y = Cl	10
5578	7-Cl-3-Me	II; X = H, Y = Cl	10
5732	7-Cl-2-Me	III; X = H, Y = Cl	80
5735	7-Cl-2 : 3-Me_2	IV; X = H, Y = Cl	>80

TABLE III.

Antimalarial activity of miscellaneous 4-aminoalkylaminoquinolines.

Ref. no.	Quinoline derivative.	Approx. M.E.D., mg./kg.
5554	4-3′-Dimethylaminopropylamino-	20
5444	4-4′-Diethylaminobutylamino-	20
5384	4-(4-Diethylamino-1-methylbutylamino)-	20
5707	4-(3-Diethylamino-1-methylpropylamino)-	<40
5555	4-(1 : 3-Bisdiethylamino-2-propylamino)-	40
5695	4-3′-Piperidinopropylamino-	>40
5474	2 : 4-Bis-(4-diethylamino-1-methylbutylamino)-	160
5702	6-Chloro-4-3′-diethylaminopropylamino-	40
5553	7-Chloro-4-2′-diethylaminoethylamino-	20
5623	7-Chloro-4-(4-diethylamino-1-methylbutylamino)-	5
5323	4-3′-Diethylaminopropylamino-7 : 8-benzo-	160
5464	4-3′-Diethylaminopropylamino-5 : 6-benzo-	160

the heterocyclic ring had reduced the therapeutic effect, least in the 3-substituted and most in the 2 : 3-disubstituted compounds. In the same test mepacrine had a minimum effective does (M.E.D.) of 40 mg./kg. of body weight, so the extra nucleus in the acridine molecule had an adverse effect whether mepacrine is regarded as a derivative of 6-methoxy- or of 7-chloroquinoline.

Experimental.

4-Chloro-2-nitropropiophenone.—To a stirred suspension of sodium methoxide (38 g.) in dry ether (550 c.c.), cooled in ice, ethyl α-methylacetoacetate (101 g.) was added, followed during 15—20 minutes by 4-chloro-2-nitrobenzoyl chloride (154 g.) in dry ether (150 c.c.), and the mixture was boiled under reflux. After 1 hour water was added to dissolve the precipitated sodium chloride and the ethereal layer was separated, dried (Na_2SO_4), and evaporated. The residual oil (160—170 g.) was refluxed with ethanol (1400 c.c.) and concentrated sulphuric acid (60 c.c.) for 7 hours and then kept overnight. Ethanol and ethyl acetate were removed by steam-distillation and the aqueous mixture was stirred and refluxed for 1—2 hours, cooled, and extracted with ether. The extract was washed with 10% sodium carbonate solution and with water, dried (Na_2SO_4), and distilled. *4-Chloro-2-nitropropiophenone* (40 g.) was obtained as an oil, b. p. 100—110°/0·25 mm., which was not further purified (Found : N, 6·7; Cl, 15·9. $C_9H_8O_3NCl$ requires N, 6·6; Cl, 16·6%), and *ethyl α-4-chloro-2-nitrobenzoylpropionate* (19 g.) as a waxy solid, b. p. 160—162°/0·25 mm., giving white tabular crystals, m. p. 71°, from methanol (Found : C, 51·0; H, 4·4; N, 5·1; Cl, 12·0. $C_{12}H_{12}O_5NCl$ requires C, 50·45; H, 4·2; N, 4·9; Cl, 12·45%).

2-Amino-4-chloropropiophenone.—4-Chloro-2-nitropropiophenone (31 g.) and 50% acetic acid (400 c.c.) were stirred and heated on the steam-bath, and iron (pin dust, 65 g.) was added cautiously during 30 minutes, water being added to make up loss by evaporation. The mixture was stirred for ½ hour longer at 100°, cooled, and extracted with ether. The extract was washed successively with sodium carbonate solution, 5% sodium hydroxide solution, and water, dried (Na_2SO_4), and evaporated. The *amine* (15 g.) crystallised from light petroleum (b. p. 60—80°) in colourless prisms with a strong sweet odour, m. p. 72—73° (Found : C, 58·55; H, 5·5; N, 7·8. $C_9H_{10}ONCl$ requires C, 58·75; H, 5·45; N, 7·6%).

4-Chloro-2-formamidopropiophenone.—2-Amino-4-chloropropiophenone (6 g.) and anhydrous formic acid (7 c.c.) were refluxed for 10 minutes. On cooling, the *formyl* derivative crystallised in fine needles which were filtered off and crystallised from ethanol as colourless prisms or needles, m. p. 86—87° (Found : N, 6·8. $C_{10}H_{10}O_2NCl$ requires N, 6·6%).

2-Acetamido-4-chloropropiophenone.—2-Amino-4-chloropropiophenone (4 g.), acetic acid (10 c.c.), and acetic anhydride (10 c.c.) were heated on the steam-bath for 2 hours and poured into water (150 c.c.), and the *amide* was collected and crystallised from ethanol; from light petroleum (b. p. 100—120°), it formed needles, m. p. 123° (Found : N, 6·1. $C_{11}H_{12}O_2NCl$ requires N, 6·2%).

4-Chloro-2-formamidoacetophenone.—2-Amino-4-chloroacetophenone (10 g.) and anhydrous formic acid (10 c.c.) were refluxed for 10 minutes. The *formyl* derivative crystallised on cooling, and gave needles (from ethanol), m. p. 123° (Found : Cl, 17·6. $C_9H_8O_2NCl$ requires Cl, 17·95%).

4-Hydroxy-3-methylquinoline.—*o*-Formamidopropiophenone (5·9 g.), ethanol (40 c.c.), water (120 c.c.), and 40% aqueous sodium hydroxide (5·2 c.c.) were refluxed for 2 hours, filtered, and acidified with acetic acid. The product (2 g.) separated slowly from the cold solution, a further crop being obtained by evaporation of the mother-liquors. It crystallised from ethanol in stout colourless prisms, m. p. 228—229° (Found : C, 75·3; H, 5·7; N, 9·1. Calc. for $C_{10}H_9ON$: C, 75·4; H, 5·65; N, 8·8%).

Cyclisation of 4-chloro-2-formamidoacetophenone.—The formyl derivative (4·3 g.), ethanol (75 c.c.), water (300 c.c.), and 40% sodium hydroxide solution (2 c.c.) were refluxed for 5 hours, the ethanol was distilled off, and the boiling solution filtered. On cooling, 2-amino-4-chloroacetophenone crystallised (1·5 g.; m. p. 88°) and was filtered off. The filtrate, acidified with acetic acid, gave a crystalline precipitate of 7-chloro-4-hydroxyquinoline (0·55 g.), m. p. 274° (Found : N, 7·7. Calc. for C_9H_6ONCl : N, 7·8%), identical with material prepared by other methods. The product was characterised by conversion into 4 : 7-dichloroquinoline, m. p. 84° (Found : Cl, 35·1. Calc. for $C_9H_5NCl_2$: Cl, 35·8%).

Cyclisation of 2-Acetamido-4-chloroacetophenone.—2-Acetamido-4-chloroacetophenone (Atkinson and Simpson, *J.*, 1947, 232) (12 g.), ethanol (240 c.c.), water (900 c.c.), and 40% aqueous sodium hydroxide (6·5 c.c.) were refluxed for 3 hours and allowed to cool overnight. The crystalline precipitate *A* (8 g.) was filtered off and the filtrate was acidified with acetic acid, giving a precipitate of 7-chloro-4-hydroxyquinaldine (0·4 g.), needles, m. p. 313—316°, from ethanol, characterised by conversion into 4 : 7-dichloroquinaldine, m. p. 101° (Found : Cl, 32·9. Calc. for $C_{10}H_7NCl_2$: Cl, 33·5%). Precipitate *A*, extracted with boiling benzene, gave a residue of 7-chloro-2-hydroxylepidine (3·8 g.), m. p. 280°, and 2-amino-4-chloroacetophenone was recovered from the benzene. In another experiment, the material precipitated by acetic acid consisted mainly of *N*-acetyl-5-chloroanthranilic acid, white needles (from ethanol), m. p. 211°, not depressed by an authentic specimen

Cyclisation of 4-Chloro-2-formamidopropiophenone.—4-Chloro-2-formamidopropiophenone (6·3 g.), ethanol (30 c.c.), water (100 c.c.), and 40% aqueous sodium hydroxide (3·3 c.c.) were refluxed for 2 hours and the ethanol was distilled off, and the solution diluted with hot water (50 c.c.) and filtered. Acidification of the filtrate with acetic acid precipitated 7-chloro-4-hydroxy-3-methylquinoline (4·6 g.) which crystallised from ethanol in white needles, m. p. 320—325° (depending on rate of heating) (Found : C, 61·95; H, 4·4; N, 8·0. Calc. for $C_{10}H_8ONCl$: C, 61·95; H, 4·15; N, 7·25%). In other experiments appreciable amounts of *5-chloro-N-formylanthranilic acid* were also formed [white needles (from ethanol), m. p. 205—207°, not depressed by admixture with a specimen prepared from 5-chloroanthranilic acid and formic acid] (Found : C, 48·4; H, 3·7; N, 7·2; Cl, 16·9. $C_8H_6O_3NCl$ requires C, 48·1; H, 3·0; N, 7·0; Cl, 17·8%).

Cyclisation of 2-Acetamido-4-chloropropiophenone.—2-Acetamido-4-chloropropiophenone (3·3 g.), ethanol (50 c.c.), water (150 c.c.), and 40% aqueous sodium hydroxide (1·5 c.c.) were refluxed for 3 hours, the ethanol removed by distillation, and the hot solution filtered from *7-chloro-4-hydroxy-2 : 3-dimethylquinoline* (0·1 g.) (laminæ, m. p. 340°, from ethanol, see below). The filtrate, on cooling, deposited

7-chloro-2-hydroxy-4-ethylquinoline (0·6 g.) which formed white needles, m. p. 261—262°, from ethanol (Found: C, 61·9 ± 1·5; H, 5·1. $C_{11}H_{10}ONCl$ requires C, 63·6; H, 4·8%. Owing to a mishap there was insufficient material for accurate analysis). Acidification of the aqueous mother-liquor precipitated *N*-acetyl-5-chloroanthranilic acid (1·8 g.), needles (from ethanol or benzene), m. p. 211° not depressed by admixture with an authentic specimen.

7-Chloro-2-hydroxylepidine.—Acetoaceto-*m*-chloroanilide (55 g.) and concentrated sulphuric acid (30 c.c.) were mixed at 0° and warmed on the steam-bath. An exothermic reaction started at 85—90°, the temperature being kept below 100° by cooling. After 2 hours at 95° the mixture was poured into water (500 c.c.) and the product collected, washed until acid-free, and crystallised from acetic acid and then from ethanol, giving colourless laminæ, m. p. 280° (C.I.B.A., *loc. cit.*, give m. p. 272°) (Found: Cl, 18·2. Calc. for $C_{10}H_8ONCl$: Cl, 18·35%).

7-Chloro-4-hydroxy-2 : 3-dimethylquinoline.—*m*-Chloroaniline (25·5 g.) and ethyl α-methylacetoacetate (28·8 g.) were boiled with chloroform until water ceased to separate from the condensate (24 hours). The chloroform was removed on the water-bath under reduced pressure and the residual oil was added to medicinal paraffin (300 c.c.) at 280°, stirred at 260° for 2—3 minutes, and cooled. After dilution with light petroleum (b. p. 100—120°) (300 c.c.), the crystalline product was filtered off and washed with light petroleum. The crude product (23 g.), m. p. 305—310°, was extracted with boiling ethanol (800 c.c.) leaving the sparingly soluble *5-chloro-4-hydroxy-2 : 3-dimethylquinoline* which crystallised from a large volume of ethanol in irregular prisms, m. p. 365—370° (Found: Cl, 16·8. $C_{11}H_{10}ONCl$ requires Cl, 17·1%). Repeated crystallisation of the more soluble fraction from ethanol gave white laminæ of 7-chloro-4-hydroxy-2 : 3-dimethylquinoline, m. p. 340—345°, not depressed by material prepared from 2-acetamido-4-chloropropiophenone (Found: N, 7·1. $C_{11}H_{10}ONCl$ requires N, 6·75%).

Condensation of p-*Anisidine with Ethyl Ethoxalylacetate.*—Commercial ethyl ethoxalylacetate (sodium salt) (70 g.), suspended in ethanol (200 c.c.), was treated at <20° with *p*-anisidine hydrochloride (54 g.) in warm ethanol (120 c.c.), kept at room temperature overnight, and poured into 30% brine (2 l.). The oil was extracted with ether (2 × 500 c.c.) and the extract washed with water (3 × 500 c.c.), dried (Na_2SO_4), and evaporated. The residual oil (57 g.) was added during 5 minutes to medicinal paraffin (400 c.c.) pre-heated to 300° and the mixture was stirred for 5 minutes at 240—245°, cooled, and diluted with light petroleum (400 c.c.; b. p. 80—100°). When cold the crystals of ethyl 4-hydroxy-6-methoxyquinoline-2-carboxylate (10 g.) were collected, washed with light petroleum, and crystallised from ethanol, forming pale yellow needles, m. p. 216° (Found: C, 63·4; H, 5·35; N, 5·9. Calc. for $C_{13}H_{13}O_4N$: C, 63·1; H, 5·26; N, 5·66%). The petroleum–paraffin mother-liquor slowly deposited *ethyl 4-ethoxy-6-methoxyquinoline-2-carboxylate* (4·5 g.) which formed fine white needles, m. p. 125°, from ethanol (Found: C, 65·1; H, 5·5; N, 5·3. $C_{14}H_{17}O_4N$ requires C, 65·4; H, 6·18; N, 5·08%). Repetition of this experiment frequently gave as a sparingly soluble by-product p-*anisidino*-N-p-*methoxyphenylmaleinimide*, yellow needles (from acetic acid), m. p. 225—226° (Found: C, 66·2; H, 5·2; N, 8·8. $C_{18}H_{16}O_4N_2$ requires C, 66·6; H, 4·95; N, 8·65%). Formation of this compound was avoided by removing free *p*-anisidine from the *p*-methoxyphenyliminosuccinic ester by washing with dilute acid before cyclisation.

In a similar manner ethyl α-ethoxalylpropionate and *p*-anisidine gave ethyl 4-hydroxy-6-methoxy-3-methylquinoline-2-carboxylate, pale yellow microscopic needles, m. p. 185—186°, from ethanol (Found: C, 59·8; H, 5·7; N, 5·4; H_2O, 6·1. Calc. for $C_{14}H_{15}O_4N,H_2O$: C, 60·2; H, 6·3; N, 5·0; H_2O, 6·45%), and 1-p-*anisidino-2-methyl-N-p-methoxyphenylmaleinimide*, flat yellow needles (from ethanol), m. p. 163—164° (Found: C, 67·2; H, 5·2; N, 8·7. $C_{19}H_{18}O_4N_2$ requires C, 67·4; H, 5·3; N, 8·3%). Unlike the compounds from *m*-chloroaniline (Surrey and Cutler, *J. Amer. Chem. Soc.*, 1946, **68**, 514) these maleinimides from *p*-anisidine were readily separated from the quinoline derivatives.

p-Anisidine (6·15 g.) and ethyl acetylenedicarboxylate (8·9 g.) in ether (70 c.c.) reacted exothermically. After refluxing for 1 hour, the ether was removed and the residual oil cyclised by being heated for 3—4 minutes in medicinal paraffin (120 c.c.) at 250°. The crystalline product was separated by crystallisation from ethanol into *p*-anisidino-*N*-*p*-methoxyphenylmaleinimide (2 g.) and ethyl 4-hydroxy-6-methoxyquinoline-2-carboxylate (5 g.).

4-Ethoxy-6-methoxyquinoline-2-carboxylic Acid.—The ester (4 g.) was refluxed for 3 hours with 10% sodium hydroxide solution (75 c.c.) and then cooled, and the sparingly soluble sodium salt was collected, dissolved in hot water (100 c.c.), and acidified. The *acid*, m. p. 212—213° (decomp.), was crystallised from water (Found: C, 60·5; H, 4·8; N, 5·5. $C_{12}H_{13}O_4N,0·5H_2O$ requires C, 60·8; H, 5·45; N, 5·45%); the *hydrochloride* formed cream-coloured needles (from 2N-hydrochloric acid), m. p. 276° (decomp.) (Found: Cl′, 10·7. $C_{12}H_{13}O_4N,HCl,2·5H_2O$ requires Cl′, 10·8%). The hydrochloride, when heated above its m. p., gave 6-methoxy-4-hydroxyquinoline, m. p. 237°.

4-Ethoxy-6-methoxyquinoline.—4-Ethoxy-6-methoxyquinoline-2-carboxylic acid was heated above its m. p. until evolution of carbon dioxide ceased, and the *product* was crystallised from light petroleum (b. p. 40—60°), giving colourless prisms, m. p. 39—40° (Found: N, 6·4. $C_{12}H_{13}O_3N$ requires N, 6·9%).

7-Chloro-2 : 4-dihydroxy-3-methylquinoline.—(*a*) *m*-Chloroaniline (63·7 g.) and ethyl methylmalonate (87 g.) were heated under a long air-condenser allowing ethanol formed in the reaction to distil off. The temperature was held at 230—240° for ½ hour, then at 290—300° for 1½—2 hours, and finally raised to 340° during ½ hour. After cooling, the glassy product was refluxed with acetone (100 c.c.) until broken down to a crystalline solid, cooled, filtered off, and washed with acetone until free from colour. The crude *product* (58·5 g.) was purified by dissolution in hot 10% sodium carbonate solution (600 c.c.), filtration, and re-precipitation with hydrochloric acid (recovery 54 g., m. p. >280°). It crystallised from butanol in faintly cream-coloured prisms sintering at 280°, m. p. 290—295° (Found: C, 57·2; H, 3·9; N, 6·9. $C_{10}H_9O_3NCl$ requires C, 57·3; H, 3·8; N, 6·7%).

(*b*) Ethyl α-(4-chloro-2-nitrobenzoyl)propionate (3 g.) was hydrogenated over Raney nickel in ethanol (H_2 uptake 700 c.c.; reduction of the nitro-group requires 770 c.c. at 25°/760 mm.), and the

filtered solution was evaporated to dryness. The gummy residue was digested with 10% aqueous sodium hydroxide (30 c.c.) at 80—90° and the solution was filtered and acidified with acetic acid to precipitate the crude product (0·6 g.), m. p. >300°, which was characterised by conversion into 2 : 4 : 7-trichloro-3-methylquinoline.

2 : 4 : 7-*Trichloro*-3-*methylquinoline*.—7-Chloro-2 : 4-dihydroxy-3-methylquinoline (3 g.) and phosphoryl chloride (12 c.c.) were heated under reflux for 3 hours, cooled, poured on ice and, when the phosphoryl chloride had decomposed, the *product* was filtered off, washed until acid-free, and dried at 60° (3·45 g.; m. p. 102—104°). It crystallised from light petroleum (b. p. 60—80°) in long colourless needles, m. p. 105—106° (Found : N, 5·6. $C_{10}H_4NCl_3$ requires N, 5·7%).

The following were prepared similarly, but were isolated by making the reaction mixture alkaline and extracting it with ether :

4 : 7-*Dichloro*-2 : 3-*dimethylquinoline*, white needles [from light petroleum (b. p. 60—80°)], m. p. 89° (Found : N, 6·35. $C_{11}H_9NCl_2$ requires N, 6·2%).

4 : 5-*Dichloro*-2 : 3-*dimethylquinoline*, needles [from light petroleum (b. p. 80—100°)], m. p. 90—91° (Found : N, 6·5.

2 : 7-Dichlorolepidine, needles [from light petroleum (b. p. 80—100°)], m. p. 97° (Found : Cl, 32·7. Calc. for $C_{10}H_7NCl_2$: Cl, 33·5%).

4 : 7-*Dichloro*-2-*hydroxy*-3-*methylquinoline*.—2 : 4 : 7-Trichloro-3-methylquinoline (3 g.), 20% hydrochloric acid (30 c.c.), and dioxan (15 c.c.) were refluxed for 6 hours, diluted with water (250 c.c.), and left overnight. The *product* (2·7 g.) was filtered off and crystallised from 2-ethoxyethanol in white needles, m. p. 276° (Found : N, 6·3. $C_{10}H_7ONCl_2$ requires N, 6·13%).

Condensation of 2 : 4-*Dihydroxyquinolines with Dialkylaminoalkylamines*.—The following 4-dialkylaminoalkylamino-2-hydroxyquinolines were prepared by the method described in Part XVII, *i.e.*, reaction of the components at 180—190° for 24—48 hours and separation of the products by dissolution in dilute acetic acid and precipitation with ammonia. They were converted into the corresponding 2-chloro-compounds by prolonged (24 hours') heating with phosphoryl chloride.

2-*Hydroxy*-4-3′-*piperidinopropylaminoquinoline*, white plates (from ethanol), m. p. 253° (Found : C, 71·3; H, 8·0; N, 14·6. $C_{17}H_{23}ON_3$ requires C, 71·5; H, 8·05; N, 14·75%).

7-*Chloro*-4-3′-*diethylaminopropylamino*-2-*hydroxy*-3-*methylquinoline*, pale yellow prisms (from ethanol), m. p. 125—126° (Found : N, 13·05, 13·2. $C_{17}H_{24}ON_3Cl$ requires N, 13·1%).

4-2′-*Diethylaminoethylamino*-2-*hydroxy*-7 : 8-*benzoquinoline*, yellow platelets (from ethanol), m. p. 228° (Found : C, 73·9; H, 7·45; N, 13·8. $C_{19}H_{23}ON_3$ requires C, 73·7; H, 7·45; N, 13·6%).

4-3′-*Diethylaminopropylamino*-2-*hydroxy*-7 : 8-*benzoquinoline*, colourless prisms (from ethanol), m. p. 242° (Found : C, 74·3; H, 7·85; N, 13·4. $C_{20}H_{25}ON_3$ requires C, 74·25; H, 7·75; N, 13·0%).

2-*Chloro*-4-3′-*piperidinopropylaminoquinoline*, white foliated plates (from aqueous ethanol), m. p. 142—143° (Found : Cl, 11·8. $C_{17}H_{22}N_3Cl$ requires Cl, 11·7%).

2-*Chloro*-4-(4-*diethylamino*-1-*methylbutylamino*)-3-*methylquinoline*, yellow oil, b. p. 184—186°/0·2 mm. (Found : N, 12·5. $C_{19}H_{18}N_3Cl$ requires N, 12·6%). The hydroxy-compound was a viscous oil which was not characterised.

2 : 7-*Dichloro*-4-3′-*diethylaminopropylamino*-3-*methylquinoline*, pale yellow solid, m. p. 52—54°, b. p. 205°/0·2 mm. (Found : Cl, 20·9. $C_{17}H_{23}N_3Cl_2$ requires Cl, 20·9%).

2-*Chloro*-4-2′-*diethylaminoethylamino*-7 : 8-*benzoquinoline*, white needles (from *cyclo*hexane), m. p. 118—119° (Found : N, 12·75. $C_{19}H_{22}N_3Cl$ requires N, 12·83%).

2-*Chloro*-4-3′-*diethylaminopropylamino*-7 : 8-*benzoquinoline*, white rhombic prisms (from *cyclo*hexane), m. p. 112° (Found : N, 12·4; Cl, 9·8. $C_{20}H_{24}N_3Cl$ requires N, 12·3; Cl, 10·4%).

7-*Chloroquinoline*-4-*sulphonic Acid*.—4 : 7-Dichloroquinoline (5 g.) was added to a solution of sodium sulphite heptahydrate (15 g.) in water (50 c.c.), made neutral to litmus with hydrochloric acid, and refluxed until no more oil was present (1½ hours), a few drops of *n*-butanol being added to prevent the volatile chloro-compound collecting in the condenser. On cooling, *sodium* 7-*chloroquinoline*-4-*sulphonate* crystallised in white needles (Found : Cl, 12·5; S, 11·8. $C_9H_5O_3NSClNa,H_2O$ requires Cl, 12·54; S, 11·3%).

The following compounds were obtained by the same procedure : 7-Iodoquinoline-4-sulphonic acid, from 4-chloro-7-iodoquinoline (Surrey and Hammer, *loc. cit.*), as yellow prisms, m. p. 318—320°. *Sodium* salt, white needles (Found : N, 3·2; I, 32·35; S, 8·5. $C_9H_5O_3NISNa,2H_2O$ requires N, 3·55; I, 32·3; S, 8·15%).

7 : 8-Benzoquinoline-4-sulphonic acid, from 4-chloro-7 : 8-benzoquinoline (reaction time 14 hours) as pale yellow microcrystalline solid, m. p. 390° (decomp.); *sodium* salt, yellow platelets (Found : S, 11·7. $C_{13}H_8O_3NSNa$ requires S, 11·4%).

2-*Hydroxyquinoline*-4-*sulphonic acid*, from 2 : 4-dichloroquinoline (reaction time 16 hours), as colourless needles, m. p. 356—358° (decomp.) (Found : N, 6·15. $C_9H_7O_4NS$ requires N, 6·2%); *sodium* salt, white needles (Found : S, 10·7. $C_9H_6O_4NSNa,3H_2O$ requires S, 10·65%).

7-Chloro-2-hydroxy-3-methylquinoline-4-sulphonic acid, from 2 : 4 : 7-trichloro-3-methylquinoline (reaction incomplete after 64 hours); *sodium* salt, long white needles (Found : N, 4·7; Cl, 11·3; S, 10·5; H_2O, 6·2. $C_{10}H_8O_4NSClNa,H_2O$ requires N, 4·5; Cl, 11·3; S, 10·2; H_2O, 5·7%).

2-*Hydroxy*-4-3′-*piperidinopropylaminoquinoline from* 2-*Hydroxyquinoline*-4-*sulphonic Acid*.—2-Hydroxyquinoline-4-sulphonic acid (3 g.), 3-piperidinopropylamine (3 c.c.), and water (10 c.c.) were heated at

TABLE IV.

4-Dialkylaminoalkylaminoquinolines.

Ref. no.	4-Substituent.	Other substituents.	Method.	Formula.	B. p. (°/mm.).	M. p.	Found, %. C.	H.	N.	Cl'.	Required, %. C.	H.	N.	Cl'.
5554	$Me_2N\cdot[CH_2]_3\cdot NH$	—	*a*	$C_{14}H_{19}N_3$	168/0·2	—	—	—	—	—	—	—	—	—
				$C_{14}H_{19}N_3,H_2O$	—	73°	67·7	8·3	16·5	—	67·9	8·5	17·0	—
5553	$Et_2N\cdot[CH_2]_3\cdot NH$	7-Cl	*a*	$C_{14}H_{18}N_3Cl$	164/0·05	—	—	—	—	—	—	—	—	—
				$C_{14}H_{20}N_3Cl,2HCl,H_2O$	—	258—259	48·7	6·6	11·4	—	48·8	6·5	11·4	—
5271	$Et_2N\cdot[CH_2]_3\cdot NH$	—	*a, b*	(see Part XVII)										
		2-Me	*a*	$C_{17}H_{25}N_3,2HCl,0·5H_2O$	—	210—212	57·7	8·5	12·4	20·2	57·8	7·9	11·9	20·1
4628	,,	3-Me	*a, b*	$C_{17}H_{25}N_3$	163/0·15	—	—	—	—	—	—	—	—	—
				$C_{17}H_{25}N_3,2HCl,0·5H_2O$	—	242—243	58·3	7·6	11·8	20·5	57·8	7·9	11·9	20·1
5284	,,	$2:3\text{-}Me_2$	*a*	$C_{18}H_{27}N_3$	162/0·18	—	—	—	—	—	—	—	—	—
				$C_{18}H_{27}N_3,2H_2SO_4,H_2O$	—	109	43·3	6·6	8·7	12·3*	43·3	6·6	8·4	12·8*
5372	,,	6-Cl	*a*	$C_{16}H_{22}N_3Cl$	168/0·05	—	—	—	—	—	—	—	—	—
				$C_{16}H_{22}N_3Cl,H_2O$	—	60	62·1	7·7	14·3	—	62·0	7·75	13·6	—
5702	,,	7-Cl	*a, c*	$C_{16}H_{22}N_3Cl$	192/0·1	54—58	65·4	7·4	14·25	—	65·85	7·55	14·4	—
				$C_{16}H_{22}N_3Cl,H_2O$	—	40—45	—	—	13·5	11·4†	—	—	13·6	11·5†
5371	,,	7-Cl 2-Me	*a*	$C_{17}H_{24}N_3Cl$	187/0·12	—	—	—	—	—	—	—	—	—
				$C_{17}H_{24}N_3Cl,2HCl,3H_2O$	—	253—254	47·4	7·5	10·5	—	47·15	7·4	9·7	—
5732	,,	7-Cl 3-Me	*a*	$C_{17}H_{24}N_3Cl$	163/0·03	—	—	—	—	—	—	—	—	—
				$C_{17}H_{24}N_3Cl,2HCl,H_2O$	—	217—218	51·2	6·8	10·4	18·7	51·4	7·05	10·6	18·0
5578	,,	7-Cl $2:3\text{-}Me_2$	*a*	$C_{18}H_{26}N_3Cl$	190/0·3	—	—	—	—	—	—	—	—	—
				$C_{18}H_{26}N_3Cl,2HCl,2H_2O$	—	233—234	50·7	7·6	9·8	17·3	50·4	7·45	9·8	16·6
5735	,,	6-MeO	*a*	$C_{17}H_{25}ON_3$	172/0·05	76—77	—	—	14·45	—	—	—	14·65	—
				$C_{17}H_{25}ON_3,H_2O$	—	60	67·3	8·6	14·0	—	66·8	8·8	13·8	—
5293	,,	6-MeO 2-Me	*a*	$C_{18}H_{27}ON_3$	193/0·2	114—115	71·3	8·6	13·95	—	71·6	8·95	13·95	—
4935	,,	6-MeO 3-Me	*a*	$C_{18}H_{27}ON_3$	184/0·13	45	—	—	—	—	—	—	—	—
5120	,,			$C_{18}H_{27}ON_3,2HCl,0·5H_2O$	—	260	57·0	7·5	10·9	—	56·4	7·3	11·0	—
5068	,,	6-MeO $2:3\text{-}Me_2$	*a*	$C_{19}H_{29}ON_3$	192/0·35	—	—	—	—	—	—	—	—	—
				$C_{19}H_{29}ON_3,2HCl,0·5H_2O$	—	245—246	57·8	7·6	10·7	18·2	57·4	8·05	10·6	17·9
5464	,,	5 : 6-benzo	*a*	$C_{20}H_{25}N_3$	180/0·005	51—54	77·8	8·05	13·7	—	78·1	8·15	13·7	—
5323	,,	7 : 8-benzo	*a, b*	$C_{20}H_{25}N_3$	200/0·08	—	—	—	—	—	—	—	—	—
				$C_{20}H_{25}N_3,H_2O$	—	75—78	73·1	7·6	13·2	—	73·7	8·3	12·9	—
5695	$CH_2{<}[CH_2]_4{>}N\cdot[CH_2]_3\cdot NH$	—	*b*	$C_{17}H_{22}N_2$	176/0·03	—	—	—	—	—	—	—	—	—
				$C_{17}H_{22}N_2,H_2O$	—	105—106	69·7	8·3	14·5	—	71·0	8·7	14·65	—
6027	,,	8-MeO	*a*	$C_{18}H_{23}ON_3$	210/0·1	165—166	—	—	14·6	—	—	—	14·05	—
5444	$Et_2N\cdot[CH_2]_4\cdot NH$	—	*a*	$C_{17}H_{23}N_3$	166/0·05	—	—	—	15·4	—	—	—	15·5	—
				$C_{17}H_{23}N_3,H_2O$	—	65—67	70·7	9·3	14·45	—	70·5	9·3	14·5	—
5707	$Et_2N\cdot[CH_2]_3\cdot CHMe\cdot NH$	—	*a*	$C_{17}H_{23}N_3$	150/0·03	—	74·1	8·0	15·2	—	75·1	9·2	15·5	—
5384	$Et_2N\cdot[CH_2]_3\cdot CHMe\cdot NH$	—	*b*	$C_{18}H_{27}N_3$	155/0·05	72—74	75·3	9·2	15·4	—	75·7	9·45	14·75	—
5469	,,	3-Me	*b*	$C_{19}H_{29}N_3,H_2O$	168/0·2	—	71·8	9·5	12·9	—	71·9	9·75	13·25	—
5623	,,	7-Cl	*a, c*	$C_{18}H_{26}N_3Cl$	187/0·09	87	67·8	7·9	13·3	—	67·55	8·15	13·45	—
5474	,,	$2\text{-}Et_2N\cdot[CH_2]_3\cdot CHMe\cdot NH$	*a*	$C_{27}H_{47}N_5$	208/0·06	—	71·4	9·4	15·0	—	73·4	10·7	15·9	—
5555	$(Et_2N\cdot CH_2)_2CH\cdot NH$	—	*a*	$C_{20}H_{32}N_2$	192/0·2	—	—	—	—	—	—	—	—	—
				$C_{20}H_{32}N_4,3HCl,4H_2O$	—	267	47·8	8·45	11·2	20·4	47·2	8·45	11·0	20·9

* Analysis for S. † Analysis for Cl.

140—150° for 8 hours. The crystalline product was filtered off when cold and crystallised from ethanol in colourless plates, m. p. 253°, not depressed on admixture with a specimen prepared from 2 : 4-dihydroxyquinoline.

Preparation of 4-Dialkylaminoalkylaminoquinolines.—The following three preparative methods were employed. (*a*) The requisite 4-chloroquinoline (0·02 mol.), dialkylamjnoalkylamine (0·04 mol.), and potassium iodide (0·1 g.) were stirred and heated at 180° for 8 hours and the product when cold was dissolved in 10% acetic acid containing 5% of sodium acetate. The solution was treated with carbon, filtered, and made strongly alkaline with sodium hydroxide, and the bases were extracted with ether. After drying (Na_2SO_4), the ether was removed, the excess of dialkylaminoalkylamine distilled off at 10—15 mm., and the residue distilled at 0·05—0·25 mm. The products were viscous oils which crystallised in some cases, or were converted into crystalline hydrates, hydrochlorides, or sulphates. (*b*) 2-Chloro-4-dialkylaminoalkylaminoquinolines, dissolved in methanol, were hydrogenated at ordinary temperature and pressure over Raney nickel. After filtration, removal of the solvent, and treatment with sodium hydroxide, the products were distilled at 0·05—0·25 mm. (*c*) 7-Chloroquinoline-4-sulphonic acid (4·7 g.), 4-diethylamino-1-methylbutylamine (6 c.c.), and water (15 c.c.) were heated at 140—150° for 8 hours in a sealed tube. When cold the mixture was made alkaline with sodium hydroxide, and the bases were extracted with ether, dried (Na_2SO_4), and distilled.

Of the 4-dialkylaminoalkylaminoquinolines listed in Table IV, numbers 4935, 5271, 5293, 5323, 5371, 5384, 5465, 5469, 5553, 5578, and 5623 have previously been described.

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Blackley, Manchester, 9. [*Received, November 15th*, 1950.]

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232. *The Stereochemistry of Steroids. Part IV. The Concept of Equatorial and Polar Bonds.**

By D. H. R. Barton and W. J. Rosenfelder.

The application of the concept of equatorial and polar bonds in steroid chemistry is outlined. The configurations assigned previously (Barton, *Experientia*, 1950, **6**, 316) to the cholestan-4-ols are confirmed. The importance of coplanarity of participating atomic centres in the elimination reactions of *cyclo*hexane derivatives is further emphasized and illustrated, *inter alia* by a study of the stereochemical aspects of the debromination of 1 : 2-dibromides. A *trans*-1 : 2-dibromide with the two C–Br bonds polar is debrominated more easily than the stereoisomeric *trans*-1 : 2-dibromide with the two C–Br bonds equatorial.

In recent years it has become generally accepted that the chair conformation of *cyclo*hexane is more stable than the boat. In the chair conformation it is possible (Hassel and Viervoll, *Acta Chem. Scand.*, 1947, **1**, 149; and earlier papers by Hassel) to distinguish two types of carbon–hydrogen bond : those which lie parallel to the three-fold axis of symmetry of the ring and those which are not so oriented. The former type have been called " polar " and the latter " equatorial " (Beckett, Pitzer, and Spitzer, *J. Amer. Chem. Soc.*, 1947, **69**, 2488).

There can be little doubt that this distinction between carbon–hydrogen bonds is of importance in considering the more subtle aspects of the stereochemistry of *cyclo*hexane and its congeners. In Part III of this series * we have shown that it is possible to correlate the reactivity or stability of a substituent at a given position in the steroid nucleus with its existence as a polar or equatorial bond. A similar correlation has recently been made by Reeves (*J. Amer. Chem. Soc.*, 1950, **72**, 1499) for a number of monosaccharides. Such correlations demand a prior knowledge of the most stable conformation of the molecule under consideration. In the case of the steroid ring system we have adopted (Barton, *loc. cit.*) the conformations shown in Figs. 1 or 2 (α-bonds broken, β-bonds full lines) depending on whether the A–B ring fusion is *trans* or *cis*. These conformations have the maximum number of *cyclo*hexane chairs; their justification is discussed in more detail elsewhere (Barton, *loc. cit.*; W. S. Johnson, *Experientia*, 1951, **7**, in the press).

Three of the more important aspects of equatorial and polar bonds are the following. (i) At a given position in (say) the steroid nucleus a substituent linked by an equatorial bond is, in general, thermodynamically more stable than the same substituent at the same carbon atom linked by a polar bond. Thus cholestan-3β-ol is more stable than cholestan-3α-ol,

* Parts I and II : Barton and Miller, *J. Amer. Chem. Soc.*, 1950, **72**, 370, 1066. Part III : Barton, *Experientia*, 1950, **6**, 316.

coprostan-3α-ol is more stable than coprostan-3β-ol, and so on. (ii) For ionic elimination reactions involving substituents on adjacent carbon atoms, the elimination proceeds most readily when the two substituents form polar bonds. This generalisation has been illustrated by Barton and Miller (*J. Amer. Chem. Soc.*, 1950, **72**, 1066) and is discussed further below. (iii) At a given position in (say) the steroid nucleus a substituent forming an equatorial bond is, in general, less hindered sterically than the same substituent at the same carbon atom forming a polar bond.

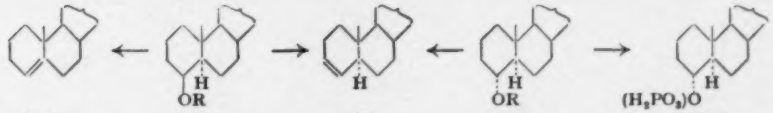
The justification for these three statements has been given in detail in Part III. In that paper we assigned configurations to the two cholestan-4-ols on the basis that the isomer, m. p. 188—189°, $[\alpha]_D$ +5°, prepared by sodium and alcohol reduction of cholestan-4-one (Windaus, *Ber.*, 1920, **53**, 488; Tschesche and Hagedorn, *ibid.*, 1935, **68**, 2251) must be cholestan-4α-ol.

FIG. 1.

FIG. 2.

Our reasoning was that this method of reduction of ketones is known to give the thermodynamically more stable epimer (Vavon, *Bull. Soc. chim.*, 1931, [iv], **49**, 937; Hückel, *Annalen*, 1937, **533**, 1) which, at the 4-position, should be the 4α-compound for this is the epimer with the hydroxyl equatorial (see Fig. 1). The second cholestan-4-ol, m. p. 131—132°, $[\alpha]_D$ +29°, prepared by catalytic hydrogenation of cholestan-4-one, was assigned the 4β-configuration. Experiments that we now report confirm our conclusions.

(a) *Elimination Evidence.*—Treatment of cholestan-4β-ol (I; R = H) with phosphorus oxychloride and pyridine at room temperature afforded pure cholest-4-ene (II), m. p. 81°, $[\alpha]_D$ +75°. The rotation was appreciably higher than is usually accepted for cholest-4-ene (about +65°), but the purity of the product was checked carefully and it was shown that cholest-4-ene of the same rotation could be obtained by regeneration from the purified dibromide. In contrast, under the same reaction conditions, cholestan-4α-ol (III; R = H) afforded no hydrocarbon. The reaction product analysed as cholestan-4α-yl dihydrogen phosphate (IV). In cholestan-4β-ol the $C_{(4)}$–OH and $C_{(5)}$–H bonds are both polar and thus the ease of elimination



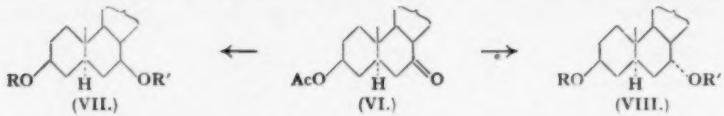
(II.) (I.) (V.) (III.) (IV.)

is explained. In cholestan-4α-ol the $C_{(4)}$–OH bond is equatorial and thus elimination is relatively difficult.

In previous papers (Barton, *J.*, 1949, 2174; Barton and Rosenfelder, *ibid.*, p. 2459) it has been demonstrated that pyrolytic elimination reactions which proceed by a molecular mechanism

are stereochemically specific in requiring a *cis*-relation of the eliminated groups. This generalisation has now been applied to the cholestan-4-yl benzoates. Pyrolysis of cholestan-4β-yl benzoate (I; R = C_6H_5·CO) afforded pure cholest-3-ene (V), with physical constants in good agreement with those reported recently by Lardelli and Jeger (*Helv. Chim. Acta*, 1949, **32**, 1817). Pyrolysis of cholestan-4α-yl benzoate gave a mixture, the rotation of which indicated that it consisted of cholest-3- (approx. 40%) and -4-ene (approx. 60%). These results are again in agreement with the assigned configurations.

(b) *Steric Hindrance Evidence.*—A comparison of the rates of alkaline hydrolysis of the cholestan-4-yl benzoates provided further confirmation for the assigned configurations.



(VII.) (VI.) (VIII.)

Cholestan-4α-yl benzoate (equatorial bond) was hydrolysed at a greater rate than cholestan-4β-yl benzoate (polar bond) (see Experimental).

Although there can no longer be any doubt as to the correctness of the configurations assigned at the 7-position in steroids (*inter al.*, Fieser, Fieser, and Chakravarti, *J. Amer. Chem.*

FIG. 3.

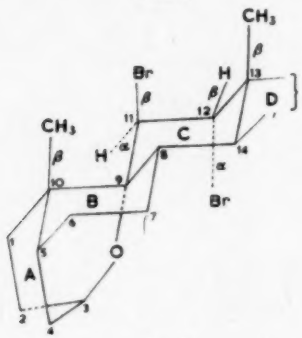


FIG. 4.

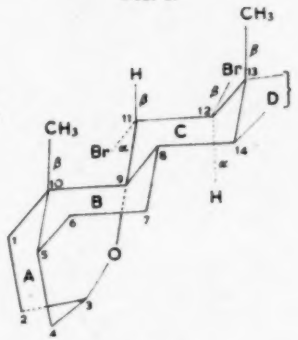


FIG. 5

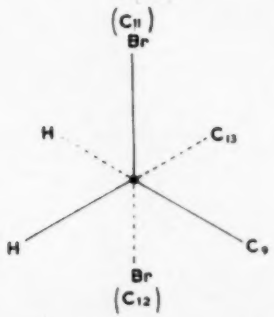
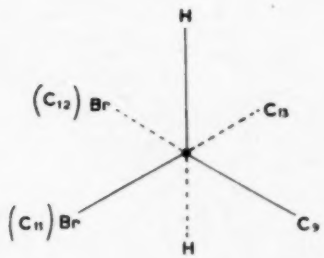


FIG. 6.



Soc., 1949, **71**, 2226; Barton, *J.*, 1949, 2174) a comprehensive correlation with the concept of polar and equatorial bonds is not possible on the basis of published evidence. We have made a number of experiments on the subject. Reduction of 7-ketocholestan-3β-yl acetate (VI) by sodium and alcohol furnished a mixture the rotation and other properties of which indicated that it consisted of 78% of cholestane-3β : 7β-diol (VII; R = R' = H) and 22% of

cholestane-3β : 7α-diol (VIII; R = R′ = H). The predominance of the former compound with the equatorial bond at $C_{(7)}$ is in agreement with our general thesis.

Comparative experiments on the rates of alkaline hydrolysis of 3β-acetoxycholestan-7α-yl and -7β-yl benzoates (VIII and VII; R = CH_3·CO, R′ = C_6H_5·CO) (see Experimental) showed that the 7β-compound, with the equatorial bond, was hydrolysed at a faster rate than the 7α-compound with the polar bond. This is an interesting result because a consideration of Stuart models could easily lead to a prediction of the opposite order.

In Part II of this series (Barton and Miller, *loc. cit.*) a study was made of the relative rates of debromination (see Table) of the two cholesteryl benzoate dibromides. It was emphasized that the results could be simply explained if elimination reactions of this type required that the four centres participating in the reaction (the two carbon atoms and the two bromine atoms) should lie, suitably disposed with respect to each other, in one plane for maximal ease of reaction. In *cyclo*hexane compounds this is equivalent to the requirement that the two groupings eliminated should be polar in the stereochemical sense. This is only possible for a dibromide which is configurationally *trans*. There is, however, an alternative conformation for a *trans*-1 : 2-dibromo*cyclo*hexane with both C–Br bonds equatorial (compare the discussion by Barton and Schmeidler, *J.*, 1948, 1197). An opportunity to test this theory further was provided by the two methyl 3α : 9α-epoxychol-11-enate dibromides, specimens of which were kindly provided by Dr. Max Tishler of Merck and Co. Inc., Rahway, New Jersey. These have been assigned the configurations 11β : 12α and 11α : 12β (Fieser and Fieser, " Natural Products Related to Phenanthrene," 3rd Edn., Reinhold Publ. Corp., 1949, p. 661) for reasons that we regard as adequate. Because of the nature of the oxide ring and of the locking of rings B, C, and D, the relative spatial positions of the atoms in the molecule are rigidly defined as shown in the conformations illustrated in Figs. 3 and 4 for the 11β : 12α- and 11α : 12β-dibromides respectively. Figs. 5 and 6 show the respective views observed on looking down the $C_{(11)}$–$C_{(12)}$ axis. In the 11β : 12α-dibromide the four centres are in one plane (two polar C–Br bonds); in the 11α : 12β-dibromide (two equatorial C–Br bonds) this is not the case. The experimental results summarised in the Table support the theory; they show that the 11β : 12α-dibromide was debrominated by iodide ion in the course of a few days, whereas the 11α : 12β-dibromide showed no indication of reaction even after six months. This is a remarkable demonstration of the influence of geometry on chemical reactivity.

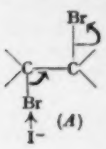
		Percentage reacted.*					
	Molarity.	15 mins.	225 mins.	15 hrs.	53 hrs.	12 days	
Cholest-2-ene dibromide	0·00758	—	—	3·4	—	22·5	46·6 (22 days)
Cholest-3-ene dibromide	0·00319	0·0	0·0	0·0	0·0	0·0	0·1 (22 days)
Cholest-4-ene dibromide	0·006475	79·7	—	100·0	—	—	—
5α : 6β-Dibromocholestan-3β-yl benzoate †	0·00611	30·1	69·8	—	—	—	—
5β : 6α-Dibromocoprostan-3β-yl benzoate †	0·00662	0·0	0·0	6·3	—	—	—
Methyl 11α : 12β-dibromo-3α : 9α-epoxycholanate	0·00677	0·0	0·0	0·0	0·0	0·0	0·1 (6 months)
Methyl 11β : 12α-dibromo-3α : 9α-epoxycholanate	0·00649	—	12·6	—	53·1	93·7	—

* For details of procedure see Exptl. All experiments at room temperature (20—25°) unless specified to the contrary.

† Data from Barton and Miller (*J. Amer. Chem. Soc.*, 1950, **72**, 1066). The figures for the 5α : 6β-compound are for 5°.

The relative rates of debromination of a number of other steroidal dibromides have also been studied (see table). From the results cholest-2-ene dibromide can be tentatively assigned the (di*p*olar) 2β : 3α-configuration, and cholest-3-ene dibromide the (diequatorial) 3β : 4α-configuration, in agreement with its complete resistance to debromination by iodide ion. In cholest-4-ene dibromide the two C–Br bonds are clearly polar but, since both the 4β : 5α- and the 4α : 5β-configurations satisfy this requirement a distinction between the two cannot be made.

It has been suggested (Young, Pressman, and Coryell, *J. Amer. Chem. Soc.*, 1939, **61**, 1640; Winstein, Pressman, and Young, *ibid.*, p. 1645) that the debromination of 1 : 2-dibromides by iodide ion is an *E*2 type elimination reaction, as illustrated in transition state (*A*).* Such a view is in agreement with our investigations of the stereochemistry of such reactions. It is of interest, however that other elimination reactions which are generally regarded (Hughes, Ingold, *et al.*, *J.*, 1948, 2117) as kinetically of the *E*1 type also show a similar geometric specificity. Examples are the solvolysis of toluene-*p*-sulphonates (Hückel, *Ber.*, 1944, **77**, 805, and papers there cited), the acid-catalysed dehydration of alcohols (Hughes, Ingold, *et al.*, *loc. cit.*), and olefin formation resulting from the action of nitrous acid on primary amines (for references to illustrative work on the menthylamines and related compounds see Simonsen and Owen, " The Terpenes," 2nd edn., Vol. 1, p. 245).



(*A*)

Experimental.

M.p.s are uncorrected. Unless specified to the contrary rotations were determined for the sodium D line in chloroform solution at room temperature, which varied from 15° to 25°. For rotation measurements all specimens were dried *in vacuo* at 20° below their m.p.s or at 110°, whichever was the lower temperature. Values of $[\alpha]_D$ have been approximated to the nearest degree.

Savory and Moore's alumina for chromatography was used in all cases unless specified to the contrary.

In the text below the phrase " in the usual way " refers to dilution with water, extraction with ether, washing successively with aqueous potassium hydroxide, aqueous hydrochloric acid, and then water, followed by evaporation of the ethereal solution *in vacuo*. Where necessary, water was removed from the residue by azeotropic distillation *in vacuo* with benzene as entrainer.

Alkaline hydrolyses were effected by using several equivalents of potassium hydroxide and refluxing the reactants for 30—60 minutes in methanolic or dioxan–methanolic solution depending on the solubility requirements of the ester.

Cholest-2-ene Dibromide.—Crude cholest-2-ene (640 mg.), prepared by the pyrolysis of cholestanyl benzoate (Barton and Rosenfelder, *J.*, 1949, 2359), in 100 ml. of 1 : 1 ether–acetic acid was brominated by addition of a slight excess of bromine in acetic acid and set aside overnight. Working up in the usual way and repeated recrystallisation from ethyl acetate–methanol gave 190 mg. of cholest-2-ene dibromide, plates, m. p. 124—124·5°, $[\alpha]_D$ +76° (*c*, 4·60). On treatment with zinc dust in acetic acid solution at water-bath temp. the dibromide was smoothly debrominated to furnish pure cholest-2-ene, m. p. 74·5—75°, $[\alpha]_D$ +69° (*c*, 1·58) (cf. Fürst and Plattner, *Helv. Chim. Acta*, 1949, **32**, 279).

The following technique was used in studying the rate of debromination of cholest-2-ene dibromide and of the other dibromides mentioned below. Approx. 0·006M-solutions of the dibromides in dry acetone (" AnalaR ") were mixed in equal volume with 0·134N-sodium iodide in the same solvent. The course of the reaction was followed from time to time by thiosulphate titration of the iodine liberated. Between titrations the solutions were kept in a dark cupboard.

Cholest-4-ene.—For the large-scale preparation of this hydrocarbon a slight modification of Hauptmann's process (*J. Amer. Chem. Soc.*, 1947, **69**, 562) was found to be suitable. Cholest-4-en-3-one (5 g.) in toluene-ω-thiol (5 ml.) was cooled to 0° and a suspension of 60% aqueous perchloric (0·5 ml.) acid in toluene-ω-thiol (4 ml.) added. The mixture was well shaken until it set solid (3 minutes). After a further 10 minutes water was added and the reaction product worked up in the usual way. Recrystallisation from benzene–methanol gave the dibenzyl mercaptal, m. p. 123—124°, in almost quantitative yield. For desulphurisation the following procedure was adopted. The benzyl mercaptal (1 g.) in dioxan (30 ml.) was refluxed for 7 hours with Raney nickel (2 g.). Benzene was then added, the nickel removed by filtration, and the reaction product worked up in the usual way. Filtration through alumina and recrystallisation from ethyl acetate–methanol furnished cholest-4-ene, m. p. 74—75°.

For the preparation of cholest-4-ene dibromide, cholest-4-ene (500 mg.) in dry ether (50 ml.) was treated with a slight excess of bromine in acetic acid (4 ml.). After 15 minutes at room temperature the ether was removed *in vacuo* at room temperature. Recrystallisation from chloroform–methanol of the crystals thus deposited gave cholest-4-ene dibromide, m. p. 116—117°, $[\alpha]_D$ +39° (*c*, 4·48), unchanged on further recrystallisation.

Treatment of this dibromide with excess of sodium iodide in acetone, working up in the usual way, and recrystallisation from ethyl acetate–methanol afforded pure cholest-4-ene, m. p. 82·5°, $[\alpha]_D$ +77° (*c*, 4·87), unchanged on further recrystallisation.

Cholestan-4α-ol.—Cholestan-4-one was prepared by a slight modification of Windaus's method (*Ber.*, 1920, **53**, 488). Cholest-4-ene (1·5 g.), suspended in glacial acetic acid (10 ml.), was treated with a mixture of fuming nitric acid (5 ml.) and glacial acetic acid (8 ml.), the addition being made with good mechanical stirring. On warming to 75° the solution cleared. It was held at this temperature for 2 hours, before being poured into water and worked up in the usual way. The reaction product (4-nitrocholest-4-ene) was not isolated in a state of purity, but was at once reduced by the Windaus (*loc. cit.*) procedure. The product of the reduction, isolated in the usual way, was chromatographed to give cholestan-4-one, eluted with benzene, and recrystallised from light petroleum (b. p. 40—60°) at −80°; it had m. p. 95—96°.

* In this transition state we regard the two carbon atoms and the two bromine atoms as lying in one plane, though this was not stated specifically in the original paper.

Reduction of cholestan-4-one by sodium and ethanol (Tschesche and Hagedorn, *Ber.*, 1935, **68**, 2251) furnished cholestan-4α-ol (from chloroform–methanol), m. p. 188—189°, $[\alpha]_D$ +5° (*c*, 1·28).

Redistilled phosphorus oxychloride (0·4 ml.) was added with cooling, to cholestan-4α-ol (90 mg.) dissolved in dry pyridine (5 ml.) and left at room temperature overnight. Dilution with water and extraction with ether revealed the absence of any neutral material. Acidification of the aqueous pyridine solution gave a precipitate of *cholestan-4α-yl dihydrogen phosphate* which, recrystallised from chloroform, decomposed at 270—290° (Found : P, 6·1. $C_{27}H_{49}O_4P$ requires P, 6·6%).

Benzoylation of cholestan-4α-ol with benzoyl chloride in pyridine at room temperature for 24 hours and working up in the usual way furnished cholestan-4α-yl benzoate (from ethyl acetate–methanol), m. p. 115—116°, $[\alpha]_D$ −20° (*c*, 3·50). Ruzicka *et al.* (*Helv. Chim. Acta*, 1944, **27**, 727) reported m. p. 117·5—118° (corr.) for this compound.

Cholestan-4β-ol.—Cholestan-4-one was hydrogenated in acetic acid according to the directions of Tschesche and Hagedorn (*loc. cit.*). Working up in the usual way afforded cholestan-4β-ol (from methanol), m. p. 131—132°, $[\alpha]_D$ +29° (*c*, 1·94), unchanged by further recrystallisation.

Cholestan-4β-ol (40 mg.) was treated with phosphorus oxychloride at room temperature overnight in the same way as the 4α-isomer (see above). The neutral product had m. p. 79—80° and, after one recrystallisation from chloroform–methanol, gave pure cholest-4-ene (20 mg.), m. p. 81°, $[\alpha]_D$ +75° (*c*, 1·21), undepressed in m. p. on admixture with cholest-4-ene regenerated from the dibromide (see above).

Benzoylation of cholestan-4β-ol with benzoyl chloride in pyridine at room temperature for 24 hours and working up in the usual way furnished *cholestan-4β-yl benzoate* (from ethyl acetate–methanol), m. p. 114·5—115·5°, $[\alpha]_D$ +57° (*c*, 2·62) (Found : C, 82·8; H, 10·4. $C_{34}H_{52}O_2$ requires C, 82·9; H, 10·5%).

Pyrolysis of Cholestan-4α-yl Benzoate.—Cholestan-4α-yl benzoate (95 mg., see above) was slowly distilled at 1 mm. pressure in a stream of dry oxygen-free nitrogen through a small electric furnace heated to 400° (time of distillation 40 minutes). The benzoic acid liberated corresponded to 99% of theory. The distillate was chromatographed when the first fraction, eluted by 30 ml. of light petroleum (b. p. 40—60°), had m. p. 71—72° unchanged on recrystallisation from ethyl acetate–methanol, $[\alpha]_D$ +69° (*c*, 1·56). The m. p. was not depressed by pure cholest-3- or -4-ene. The optical rotation indicates that the hydrocarbon mixture consisted of about 40% of cholest-3-ene and 60% of cholest-4-ene.

Pyrolysis of Cholestan-4β-yl Benzoate.—Cholestan-4β-yl benzoate (100 mg.) (see above) was pyrolysed as was the 4α-isomer (see above). The benzoic acid liberated corresponded to 98% of theory. The distillate was chromatographed, the first fraction, eluted by 30 ml. of light petroleum (b. p. 40—60°), having m. p. 71—72°. A second fraction contained no hydrocarbon. Recrystallisation from ethyl acetate–methanol gave pure cholest-3-ene, m. p. 72—72·5°, $[\alpha]_D$ +57° (*c*, 1·88), +57° (*c*, 1·37), depressed in m. p. to 69° by admixture with pure cholest-4-ene (see above).

Alkaline Hydrolysis of the Cholestan-4-yl Benzoates.—Cholestan-4α-yl benzoate (64 mg.) in dioxan (10 ml.) and ethanol (10 ml.) was treated with 10 ml. of 0·0855N-ethanolic potassium hydroxide and the mixture left at room temperature for 7 days. The total steroidal product, worked up in the usual way, had $[\alpha]_D$ −5·1° (*c*, 2·03), from which figure it can be calculated that 56% of the ester had been hydrolysed.

Cholestan-4β-yl benzoate (62·9 mg.) was simultaneously treated in the same way. The rotation of the reaction product was $[\alpha]_D$ +46·9° (*c*, 2·38), from which it can be calculated that 36% of the ester had been hydrolysed.

Cholest-3-ene Dibromide.—Pure cholest-3-ene (23·5 mg.), prepared as described above, was dissolved in dry ether (5 ml.) and treated with a 2% solution (0·5 ml.) of bromine in acetic acid at room temperature for 15 minutes. Removal of the ether *in vacuo* and addition of methanol afforded the crude dibromide, m. p. 121—122° {$[\alpha]_D$ −3° (*c*, 0·60) unchanged after 6 days at room temperature}. Recrystallisation from ethyl acetate–methanol furnished pure *cholest-3-ene dibromide*, m. p. 124—124·5°, in long needles (Found : Br, 30·15. $C_{27}H_{46}Br_2$ requires Br, 30·2%).

Reference has already been made to the preparation of cholest-2-ene dibromide (see above) from the cholestene prepared by the pyrolysis of cholestanyl benzoate. The mother-liquors from the crystallisation of this dibromide were evaporated to dryness *in vacuo* and the residue was refluxed with potassium iodide (3 g.) in dry " AnalaR " acetone (250 ml.) for 6 hours. After being worked up in the usual way ($Na_2S_2O_3$ wash) the product was dissolved in 100 ml. of 1 : 1 ether–acetic acid and treated with 100 mg. of CrO_3 at 37° for 30 minutes. The excess of chromic acid was destroyed by methanol, and the product isolated in the usual way. It was dissolved in light petroleum (b. p. 40—60°) and chromatographed over alumina. The easily eluted fractions, recrystallised from ethyl acetate–methanol, gave long needles, m. p. 121—122°, $[\alpha]_D$ +6° (*c*, 4·45), showing a marked depression in m. p. with cholest-2-ene dibromide but no depression with cholest-3-ene dibromide. Further treatment with sodium iodide in acetone and recrystallisation from ethyl acetate–methanol afforded pure cholest-3-ene dibromide, m. p. 123—124°, $[\alpha]_D$ +6° (*c*, 1·53), +6° (*c*, 1·85). The identity of the dibromide was checked by debromination with zinc dust in acetic acid solution on the water-bath, which afforded pure cholest-3-ene, m. p. 74·5—75°, depressed to 64—65° on admixture with cholest-2-ene, but undepressed on admixture with cholest-3-ene of established constitution (see above).

Reduction of 3β-Hydroxycholestan-7-one.—7-Ketocholestanyl acetate (600 mg.), m. p. 149—150°, prepared and purified as described by Barton and Cox (*J.*, 1948, 783), was dissolved in *n*-propanol (25 ml.) and reduced under reflux by the addition of sodium (2·5 g.) during 1·5 hours. The solution was refluxed for a further 1·5 hours to ensure complete dissolution of the sodium and then poured into water. Working up in the usual way, and drying the residue azeotropically, gave a mixture, m. p. 148—152°, $[\alpha]_D$ +43° (*c*, 2·48), of cholestan-3β : 7α- and -3β : 7β-diol. That the reduction was complete was shown by tests (negative) with 2 : 4-dinitrophenylhydrazine. On trituration with light petroleum (b. p. 40—60°), the mixture had unchanged m. p., and $[\alpha]_D$ +40° (*c*, 6·55). Authentic cholestan-3β : 7α-

and -3β : 7β-diol, prepared according to Wintersteiner and Moore (*J. Amer. Chem. Soc.*, 1943, **65**, 1503), had m. p. 149—150°, $[\alpha]_D$ +12° (*c*, 4·53), +12° (*c*, 2·44), and m. p. 167—168°, $[\alpha]_D$ +52° (*c*, 5·02), respectively. From these rotations the mixture of diols, $[\alpha]_D$ +43°, obtained by reduction contained 78% of the 3β : 7β-diol. This was confirmed by dissolving the correct proportions of the two authentic diols in a little dioxan and precipitation with excess of water. The m. p. of the mixture was 148—151°, undepressed on admixture with the reduction product, m. p. 148—152°, $[\alpha]_D$ +43°.

The reduction product, m. p. 148—152°, $[\alpha]_D$ +43°, was acetylated with pyridine and acetic anhydride at room temperature for 24 hours. Working up in the usual way gave a colourless oil, $[\alpha]_D$ +35° (*c*, 8·63). If the rotations of +55° (m. p. 81—87°) and −17° (m. p. 64—69°) recorded by Wintersteiner and Moore (*loc. cit.*) are accepted for the respective diacetates of the 3β : 7β- and 3β : 7α-diols, this rotation corresponds to 72% of the diacetate of cholestan-3β : 7β-diol.

Alkaline Hydrolysis of the Cholestan-3β : 7-diol 3-Acetate 7-Benzoates.—3β-Acetoxycholestan-7α-yl and -7β-yl benzoates were prepared as described previously (Barton and Rosenfelder, *loc. cit.*) and 0·0122M-solutions of the two benzoates were made up in absolute ethanol. 100-Ml. portions of the two solutions were mixed with the same volume of 0·0968N-ethanolic potassium hydroxide and heated under reflux. From time to time approx. 25-ml. portions were withdrawn and diluted with water, excess of dilute hydrochloric acid was added, the whole was extracted with benzene, and the extracts were washed further with aqueous sodium hydrogen carbonate and then water. Evaporation of the benzene extracts *in vacuo* gave in each case a solid product. This was dried *in vacuo* and a part weighed for the determination of the rotation. The following results were obtained.

Time of reflux, hours :		0·5	3·0	6·0	11·0	23·0	35·0	72·0
3β-Acetoxy-7α-yl benzoate ...	$[\alpha]_D$	−10·5°	−9·0°	−8·2°	−7·6°	−4·3°	+0·6°	+6·9°
	c	3·71	4·35	4·06	3·68	3·94	3·40	2·92
Hydrolysed, %		—	8	12	14	29	51	78
3β-Acetoxy-7β-yl benzoate ...	$[\alpha]_D$	+82·3°	+80·1°	+76·8°	+70·7°	+61·6°	+52·5°	—
	c	3·94	3·84	3·68	3·68	3·08	3·12	—
Hydrolysed, %		—	9	20	40	70	100	—

The 3β-acetate residue is rapidly hydrolysed during the first ½ hour's refluxing. Therefore the rotations of the two alcohols, 3β-hydroxycholestan-7α- and -7β-yl benzoates, can be estimated by extrapolation of the above recorded rotations to zero time to be −10·8° and +82·8° respectively. The first of these figures can be checked, for Wintersteiner and Moore (*J. Amer. Chem. Soc.*, 1950, **72**, 1923) have found the rotation of the pure compound to be −11° with which our extrapolated value is in excellent agreement. When the rotations of the cholestan-3β : 7α- and -3β : 7β-diols are taken as +11·5° and +52·3° respectively (see above), the % hydrolysis of the 7-benzoate grouping can readily be calculated from the observed rotations. This procedure is justified because the hydrolysis of the 7-benzoate residue is so slow relative to that of the 3-acetate grouping.

Debromination of the Stereoisomeric 11 : 12-*Dibromides.*—For the rates of debromination see Table. Methyl 11α : 12β-dibromo-3α : 9α-epoxycholanate, recrystallised from chloroform–methanol, had m. p. 122—122·5°, $[\alpha]_D$ +18° (*c*, 2·97). Kendall *et al.* (*J. Biol. Chem.*, 1946, **164**, 583) reported m. p. 123—124·6°, $[\alpha]_D$ +21°, for this compound. The dibromide showed no mutarotation in chloroform during 7 days at room temperature.

Methyl 11β : 12α-dibromo-3α : 9α-epoxycholanate, recrystallised from chloroform–methanol, had m. p. 140·5—141°, $[\alpha]_D$ +45° (*c*, 3·56). Kendall *et al.* (*loc. cit.*) reported m. p. 142·5—143°, $[\alpha]_D$ +45°. The dibromide showed no mutarotation in chloroform during 7 days at room temperature.

After being kept at room temperature in acetone with excess of sodium iodide for 13 days the 11β : 12α-dibromide (over 90% debrominated, see table) was worked up by pouring the mixture into water, extraction with ether, and washing with sodium thiosulphate. Evaporation of the ether gave a partly crystalline residue which was characterised by bromination according to the directions of Kendall *et al.* (*J. Biol. Chem.*, 1946, **164**, 583) for methyl 3α : 9α-epoxychol-11-enate. In this way a 55% yield of the 11β : 12α-dibromide, recrystallised from chloroform–methanol, m. p. 139—140°, $[\alpha]_D$ +43° (*c*, 3·01), and undepressed in m. p. on admixture with starting material, was obtained. Kendall *et al.* (*loc. cit.*) reported a 57% yield for reaction under the same conditions.

We are much indebted to Dr. Max Tishler of Merck and Co. Inc., Rahway, New Jersey, and Dr. E. B. Hershberg of the Schering Corp., Bloomfield, New Jersey, for specimens of the two 11 : 12-dibromides. We thank the Government Grants Committee of the Royal Society and the Central Research Fund of London University for financial assistance and the Chemical Society for a grant.

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[*Received, December 21st*, 1950.]

233. *The Synthesis of Hydrocarbons of High Molecular Weight. Part I. Monoalkylnaphthalenes.*

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The synthesis of a series of alkylnaphthalenes with side chains containing 8, 10, 12, and 18 carbon atoms is described. The 1-2′-naphthylalkanes were prepared by the reduction of the corresponding *n*-alkyl 2-naphthyl ketones, obtained by Friedel–Crafts acylation of naphthalene. Some 2′-naphthylalkanes with chains branched on the carbon atom α to the nucleus were obtained by the Grignard reaction on suitable ketones prepared as above. Three methods of synthesis of the *n*-alkyl 1-naphthyl ketones were investigated: the reaction between (i) di-1-naphthylcadmium and acyl chlorides, (ii) 1-naphthonitrile and alkylmagnesium halides, and (iii) alkyl cyanides and 1-naphthylmagnesium bromide, the last of which gave the highest yields increasing as the chain length increased. Catalytic reduction of these ketones yielded the corresponding 1-1′-naphthylalkanes. 1 : 6-Di-2′-naphthylhexane was obtained from the diketone resulting from the Friedel–Crafts reaction between tetralin and polymeric adipic anhydride.

The synthesis of a series of hydrocarbons of high molecular weight has been undertaken with the object of determining their physical constants, which should be of value in establishing some relation between the structure of these compounds and their chemical and physical properties. In this paper, the syntheses are recorded; the correlation between structure and properties will be published elsewhere.

(A) 1-2′-*Naphthylalkanes with Side Chains containing* 8, 10, 12, *and* 18 *Carbon Atoms.*—Since it was desired to synthesise alkylnaphthalenes of considerable chain length, methods useful for the preparation of lower members were not applicable in this case (cf. Smith *et al.*, *J. Inst. Pet.*, 1949, **35**, 103). Direct alkylation by the Friedel–Crafts reaction is well known to cause isomerisation, however, even under mild conditions.

The acylation of naphthalene has been used extensively in the present work, since the reduction of the ketones obtained forms a convenient method of synthesis of the alkylnaphthalenes. The somewhat conflicting results concerning the ratio of 1- to 2-ketones when different solvents are used are discussed by Smith *et al.* (*loc. cit.*). Buu-Hoï and Cagniant (*Bull. Soc. chim.*, 1945, **12**, 307) showed that high yields of ketones resulted from the Friedel–Crafts reaction with higher fatty acid chlorides, nitrobenzene being used as solvent. However, the position of the acyl group was merely assumed from analogy with the lower members: this assumption has been verified for those ketones used as intermediates in the present work. Of interest in this connection is the observation that the proportion of 1-isomer formed in carbon disulphide solution decreases with an increase in the chain length of the acyl group. In acetylation the reaction yields approximately 50% of the 1-isomer; the hexoylation of naphthalene in carbon disulphide solution yielded an appreciable amount of the 1-isomer, although the proportion of 1- to 2-isomer is much less than with the acetylation. In confirmation of this decrease, Seidel and Engelfried (*Ber.*, 1936, **69**, 2567) record the formation of only about 20% of 1-stearoylnaphthalene in the mixture of ketones formed in this solvent.

2-Naphthyl *n*-nonyl, *n*-undecyl, and *n*-heptadecyl ketones were prepared in yields of 50—70% by the method of Buu-Hoï and Cagniant (*loc. cit.*), the yield being improved by the use of aluminium chloride in a molecular proportion of 1 : 1. The purification of the 2-ketones from the small amount of the 1-isomers presented few difficulties since the former have higher m. p.s and are less soluble in organic solvents. The ketones were characterised as their 2 : 4-dinitrophenylhydrazones and azines. Proof of the structure of the ketones was obtained by selenium dioxide oxidation to 2-naphthoic acid (Smith *et al.*, *loc. cit.*). In order to determine the best method of reduction of the higher members of this series of ketones, the Clemmensen reduction and the Huang-Minlon reaction were investigated. The former was successful in all cases, although the yields decreased from approximately 56% with the *n*-heptyl ketone to 33% with the *n*-heptadecyl ketone, even with up to 18 hours' heating under reflux. We found that the Huang-Minlon reaction conditions applicable to the lower ketones gave poor results with the higher members; in view of this, the initial hydrazone formation was investigated. Each of

the prepared ketones, in boiling ethanol and with an excess of hydrazine hydrate, gave the azine, $C_{10}H_7{\cdot}C(C_nH_{2n+1}){:}N{\cdot}N{:}C(C_nH_{2n+1}){\cdot}C_{10}H_7$, and no hydrazone could be isolated.

When 3 hours' heating was allowed for hydrazone formation in the presence of a large excess of hydrazine hydrate, followed by 12 hours' heating under reflux, however, high yields of hydrocarbons were obtained, identical with the products from the Clemmensen reduction. No azine, or unsaturated compound formed by the elimination of nitrogen at the high temperatures involved, was found, although some unchanged ketone could be detected.

None of the 2-alkylnaphthalenes prepared gave complexes with picric acid, styphnic acid, or *s*-trinitrobenzene. Two of these hydrocarbons are recorded in the literature. Petrov and Andreev (*J. Gen. Chem. U.S.S.R.*, 1942, **12**, 95) claimed the synthesis of 1-2′-naphthyloctane by the Friedel–Crafts alkylation of naphthalene in *cyclo*hexane solution in the cold to minimise the isomerisation of the *n*-octyl chain. From the quoted physical constants, however, it is evident that extensive isomerisation did occur. Mikeska (*J. Org. Chem.*, 1937, **2**, 499) reported the synthesis of 1-2′-naphthyloctadecane by the Friedel–Crafts reaction in carbon disulphide solution, but since he stated that no attempt was made to separate the isomeric ketones, the hydrocarbon was certainly a mixture of 1- and 2-naphthyloctadecanes. After the completion of this work, Hart and Robinson (*J. Amer. Chem. Soc.*, 1948, **70**, 3731) described the synthesis of 1-2′-naphthyl-butane, -pentane, and -decane by the general method of Smith and Lo (*ibid.*, p. 2209). Neither refractive index nor melting point is in agreement with the values obtained in the present work. The values quoted by Hart and Robinson, being considerably lower, would suggest that the final stage of their preparation, that of dehydrogenation, was incomplete. These authors record the m. p. of the picrates of all of their hydrocarbons, but state that none was analysed. Not even the *s*-trinitrobenzene complex of 1-2′-naphthyldecane could be obtained in the present investigation, and Smith *et al.* (*loc. cit.*) state that no picrate formation occurred with the pentane derivative. Luther and Wächter (*Ber.*, 1949, **82**, 161) describe the synthesis of 1-2′-naphthyloctane by a method identical with that of Hart and Robinson; although the refractive indices they record agree with ours, yet the m. p. they give is much lower than that obtained by us.

(B) *2′-Naphthylalkanes with Branched Side Chains.*—The readily obtainable *n*-alkyl 2-naphthyl ketones were used as starting materials. 2-Naphthyl *n*-propyl ketone with *n*-butylmagnesium bromide yielded 4-2′-naphthyloctan-4-ol. The same ketone, by reaction with *n*-hexylmagnesium bromide, gave 4-2′-naphthyldecan-4-ol. In a similar manner, 6-2′-naphthyldodecan-6-ol was prepared from 2-naphthyl *n*-pentyl ketone and *n*-hexylmagnesium bromide. The same ketone afforded with ethylmagnesium chloride 3-2′-naphthyloctan-3-ol. In some cases, the crude carbinol contained some of the corresponding olefin.

Carbinol and carbinol–olefin mixture were dehydrated with anhydrous copper sulphate, and the olefins hydrogenated with Raney nickel as catalyst at 4 atm. and room temperature, giving 3-2′-naphthyloctane, 4-2′-naphthyl-octane, -decane, and -dodecane, and 6-2′-naphthyldodecane.

No complexes with picric acid, styphnic acid, or *s*-trinitrobenzene could be obtained from these hydrocarbons. On attempted crystallisation at low temperature, all of them set to glasses at about −60°.

(C) *1-1′-Naphthylalkanes.*—In view of the decreasing yields obtained by Nunn and Henze (*J. Org. Chem.*, 1947, **12**, 540) in the preparation of the lower members of the alkyl 1-naphthyl ketones as the series was ascended, and the poor yields reported by Smith *et al.* in similar reactions, the synthesis of the higher 1-naphthyl ketones by a new approach, using di-1-naphthylcadmium, was investigated. With this reagent, *n*-heptyl 1-naphthyl ketone was obtained from *n*-octanoyl chloride in 60% yield, and the *n*-nonyl ketone in 56% yield from *n*-decanoyl chloride. This decrease in yield was also apparent in the case of the further two members of the series, 1-naphthyl *n*-undecyl and *n*-heptadecyl ketones being obtained in yields of 50% and 40%, respectively. The last two ketones are recorded in the literature (Ryan and Nolan, *Proc. Roy. Irish Acad.*, 1912, **30**, *B*, 1; Ralston and Christensen, *Ind. Eng. Chem.*, 1937, **29**, 194; Turkiewicz, *Ber.*, 1940, **73**, 861; Mikeska *et al.*, *J. Org. Chem.*, 1937, **2**, 499; Seidel and Engelfried *Ber.*, 1936, **69**, 2567), but the constants quoted differ from those in this work.

As an alternative method of synthesis of these ketones, the Grignard reaction was investigated. In the preparation of *n*-heptyl 1-naphthyl ketone from 1-naphthonitrile and *n*-heptylmagnesium bromide, the general procedure of Nunn and Henze (*loc. cit.*) and of Radcliffe, Sherwood, and Short (*J.*, 1931, 2293) was followed. Radcliffe *et al.* give no details concerning the isolation of the ketones, and Nunn and Henze state that all the ketones were isolated by extracting the organic layer of the reaction product, after decomposition with aqueous ammonium chloride, by means of dilute sulphuric acid, and hydrolysing the ketimine by boiling the acid

solution. In the present instance, this procedure yielded no ketone whatsoever. When the toluene layer was heated under reflux with 10N-sulphuric acid and the resulting organic layer was treated in the normal way, the pure ketone was obtained in 50% yield, the melting point and refractive index being in agreement with the values obtained from the di-1-naphthylcadmium reaction. The yield is considerably higher than that expected from Nunn and Henze's results, and it would appear that their yields are not indicative of the extent of reaction.

The alternative Grignard method (condensation of 1-naphthylmagnesium bromide with the alkyl cyanide) has been described in certain cases by Ralston and Christensen (*loc. cit.*) and Turkiewicz (*loc. cit.*), who record high yields of ketones. By this method, ketones in yields increasing from 76 to 80% as the chain length increased have been obtained in this work. Similarly, no ketimine could be extracted from the reaction product.

All attempts to prepare the 2 : 4-dinitrophenylhydrazones, semicarbazones and phenylsemicarbazones resulted in formation of oils, the only indication of reaction being the reddish colour produced with 2 : 4-dinitrophenylhydrazine sulphate solution. This lack of reactivity of the 1-naphthyl ketones has been noted by Ryan and Nolan and by Smith *et al.* in the case of 1-naphthyl *n*-heptadecyl and pentyl ketones, respectively, the latter authors proving the presence of the carbonyl group by the infra-red spectrum. In the present work, the presence of the carbonyl group in *n*-heptyl 1-naphthyl ketone was shown by the infra-red spectrum band at 1698 ν. In view of this lack of reactivity of the series of ketones, the failure of chemical methods of reduction was not surprising. However, by catalytic reduction with copper chromite at a high temperature and pressure, 1-1′-naphthyl-octane, -decane, -dodecane, and -octadecane were obtained in excellent yield. Luther and Wächter (*loc. cit.*) have prepared the 1-naphthyloctane from 1-tetralone by the Grignard synthesis, but their value of the refractive index does not agree with ours.

None of the hydrocarbons formed complexes with picric or styphnic acids, or with *s*-trinitrobenzene.

(D) 1 : 6-*Di*-2′-*Naphthylhexane*.—To prepare a dinaphthyl hydrocarbon of comparable molecular weight, with the nuclei occupying positions at the ends of the aliphatic chain, the Friedel–Crafts reaction between polymeric adipic anhydride and tetralin was used. When the reaction was conducted in carbon disulphide solution, decomposition of the product led to an intractable tar, together with a small amount of adipic acid. Steam-distillation of the tar yielded unchanged tetralin, which was shown to contain 6-acetyltetralin, isolated as its 2 : 4-dinitrophenylhydrazone. The Friedel–Crafts reaction was repeated with benzene as solvent, and yielded a keto-acid and a diketone, later proved to be δ-(5 : 6 : 7 : 8-tetrahydro-2-naphthoyl)-valeric acid and 1 : 4-di-(5 : 6 : 7 : 8-tetrahydro-2-naphthoyl)butane, respectively. Both these substances were characterised as their 2 : 4-dinitrophenylhydrazones. The products were obtained in 30% yield, and in the proportion required by theory for the breaking of the –OC·O·CO– groups in both of the two possible ways. The recovered excess of tetralin again contained the 6-acetyl derivative. The formation of this material may be explained by the reaction of the terminal acetyl groups formed on the polymeric adipic anhydride when acetic anhydride is used as the dehydrating agent (Hill and Carothers, *J. Amer. Chem. Soc.*, 1932, **54**, 1569). 1 : 6-Di-(5 : 6 : 7 : 8-tetrahydro-2-naphthyl)hexane was obtained from the 1 : 6-diketone by the Huang-Minlon reaction, and catalytic dehydrogenation gave 1 : 6-di-2′-naphthylhexane in good yield. Although no complex with picric acid could be obtained, the hydrocarbon was characterised as its mono-*s*-trinitrobenzene complex.

Experimental.

(M. p.s are uncorrected. Analyses are by Mr. F. C. Hall and Drs. Weiler and Strauss, Oxford.)

(A) 1-2′-*Naphthylalkanes*.—n-*Alkyl 2-naphthyl ketones*. *n*-Heptyl 2-naphthyl ketone was prepared by the general method of Buu-Hoï and Cagniant (*loc. cit.*), finely powdered anhydrous aluminium chloride (80 g., 1·1 mols.) being added in portions (10 g.) to a stirred solution of naphthalene (64 g., 1 mol.) and *n*-octanoyl chloride (90 g., 1·1 mols.) in dry nitrobenzene (270 c.c.), cooled to −5°. The complex was decomposed next morning by ice and concentrated hydrochloric acid, and the nitrobenzene removed from the washed and dried (Na_2SO_4) solution by distillation *in vacuo*. The crude ketone was distilled, redistilled (b. p. 219—221°/10 mm.), and crystallised twice from ethanol, the pure material being obtained as plates, m. p. 56—57°, in 50% yield (63 g.). Buu-Hoï gives m. p. 56°. The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate as orange-red plates, m. p. 163° (Found : C, 66·4; H, 6·0. $C_{24}H_{28}O_4N_4$ requires C, 66·4; H, 6·0%). The *hetazine*, obtained by refluxing an aqueous solution of hydrazine sulphate (4 mols.) containing excess of sodium acetate with the ketone (1 mol.) in ethanol for 1 hour, crystallised from ethanol in yellow prisms, m. p. 70° (Found : N, 5·6. $C_{56}H_{44}N_2$ requires N, 5·6%).

The following ketones and their derivatives were prepared by the above methods. 2-Naphthyl *n*-nonyl ketone, 54% yield, plates, m. p. 52—53° (Buu-Hoï gives 52°); 2 : 4-*dinitrophenylhydrazone*, red plates, m. p. 139° (Found : N, 12·3. $C_{28}H_{30}O_4N_4$ requires N, 12·1%); *hetazine*, yellow prisms, m. p. 68—69° (Found : N, 5·3. $C_{29}H_{32}N_2$ requires N, 5·0%). 2-Naphthyl *n*-undecyl ketone, 60% yield, elongated prisms, m. p. 48° (Buu-Hoï gives 48°); 2 : 4-*dinitrophenylhydrazone*, orange-red plates, m. p. 119—120° (Found : C, 68·5; H, 6·8. $C_{32}H_{38}O_4N_4$ requires C, 68·6; H, 6·9%); *hetazine*, long yellow prisms, m. p. 76° (Found : N, 4·3. $C_{44}H_{56}N_2$ requires N, 4·5%). *n*-Heptadecyl 2-naphthyl ketone, 74% yield, amorphous solid, m. p. 66° (Buu-Hoï gives 66°); 2 : 4-*dinitrophenylhydrazone*, red plates, m. p. 118° (Found : N, 10·0. $C_{34}H_{44}O_4N_4$ requires N, 9·8%); *hetazine*, yellow prisms, m. p. 55° (Found : N, 3·5. $C_{46}H_{64}N_2$ requires N, 3·6%).

Degradation of n-*alkyl* 2-*naphthyl ketones to* 2-*naphthoic acid*. The method of Smith *et al.* (*loc. cit.*) using selenium dioxide and a dioxan solution of the ketone was adopted. The acidic material so obtained was crystallised from aqueous ethanol, and melted at 183—184°, undepressed by admixture with 2-naphthoic acid. The yield of acid obtained decreased from 30% with the *n*-heptyl ketone to 15% with the *n*-heptadecyl ketone.

1-2′-*Naphthylalkanes*. (*a*) Clemmensen method. The ketone (20 g.) was added to a mixture of amalgamated granulated zinc (100 g.), concentrated hydrochloric acid (100 c.c.), and water (75 c.c.), and the mixture heated under reflux for 18 hours, additional acid (90 c.c.) being added every 6 hours. The cold reaction mixture was decanted from the zinc, which was washed with warm benzene. The hydrocarbon was extracted from the aqueous layer with benzene, and the combined extracts were washed with water and dried (Na_2SO_4). Removal of the solvent followed by distillation gave the crude hydrocarbon, which was purified by distillation over sodium, followed by crystallisation from acetone or ethanol at −60° in the case of the lower members. In the reduction of the *n*-heptadecyl ketone, the method was modified by passing a continuous stream of hydrogen chloride through the reaction mixture during refluxing, and using toluene as an immiscible solvent. 1-2′-Naphthyloctane (56% yield) a colourless solid from acetone, had m. p. 13°, n_D^{20} 1·5511 (Found : C, 89·8; H, 10·0. Calc. for $C_{18}H_{34}$: C, 90·0; H, 10·0%). Luther and Wächter (*loc. cit.*) give m. p. −3·3°, n_D^{20} 1·55106; Petrov and Andreev (*loc. cit.*) give m. p. −45°, n_D^{20} 1·5510. 1-2′-Naphthyldecane, 54% yield, m. p. 19·5—19·6° (from ethanol), n_D^{20} 1·5440 (Found : C, 89·6; H, 10·2. Calc. for $C_{20}H_{32}$: C, 89·6; H, 10·4%). Hart and Robinson (*loc. cit.*) give m. p. 13°, n_D^{20} 1·5394. 1-(2′-*Naphthyl*)*dodecane*, 50% yield, m. p. 26° (from ethanol), n_D^{20} 1·5339 (Found : C, 89·2; H, 10·7. $C_{22}H_{32}$ requires C, 89·2; H, 10·8%). 1-2′-*Naphthyloctadecane*, 33% yield, m. p. 54° (from ethanol) (Found : C, 88·4; H, 11·5. $C_{28}H_{44}$ requires C, 88·4; H, 11·6%).

(*b*) Huang-Minlon method. The ketone (10 g.) was added to a solution of sodium (2·5 g.) in diethylene glycol (70 c.c.), together with hydrazine hydrate (5 c.c. of 90%). After 3 hours' heating under reflux to form hydrazone, the temperature of the reaction mixture was raised to 220°, and heating then continued for a further 12 hours, during which the upper layer of hydrazone changed from orange-red to almost colourless, with a pale blue-purple fluorescence. After cooling, the mixture was acidified with dilute hydrochloric acid, and extracted with benzene. After removal of the solvent from the washed and dried solution, the crude product was purified by the method described under (*a*). The pure products, which were identical with the materials described above, were obtained in the following yields: 1-2′-naphthyloctane, 75%; -decane, 74%; -dodecane, 75%; -octadecane, 71%.

(B) *Branched-chain* 2′-*Naphthylalkanes*.—These hydrocarbons were all prepared by the same method, given in detail for one only.

4-2′-*Naphthyloctan*-4-*ol*. 2-Naphthyl *n*-propyl ketone (Smith *et al.*, *loc. cit.*; 25 g., 0·5 mol.) in dry ether (150 c.c.) was added slowly to a stirred solution of *n*-butylmagnesium bromide (1·1 mols.; from *n*-butyl bromide 42 g., magnesium 6·7 g., and dry ether 125 c.c.). After being left overnight at room temperature, the reaction mixture was cooled in an ice–water bath, and decomposed by careful addition of sulphuric acid (20%). The separated ethereal layer was washed, dried (Na_2SO_4), and fractionated, giving 4-2′-*naphthyloctan*-4-*ol*, b. p. 138—139°/0·4 mm., n_D^{20} 1·5692, in 74% yield (23·5 g.) (Found : C, 84·3; H, 9·3. $C_{18}H_{34}O$ requires C, 84·4; H, 9·4%).

4-2′-*Naphthyloct*-3- *and* -4-*ene*. The carbinol (20 g.) was heated with anhydrous copper sulphate (2 g.) in an oil-bath at 175° for 1 hour. The cooled mixture was extracted with ether, and fractionation of the extract yielded the *octenes* as a colourless oil, b. p. 130—131°/0·5 mm., n_D^{20} 1·5857 (85% yield, 15·8 g.) (Found : C, 91·1; H, 9·3. $C_{18}H_{32}$ requires C, 90·8; H, 9·2%).

4-2′-*Naphthyloctane*. The olefin (14 g.) in ethanol (25 c.c.) was hydrogenated with Raney nickel under Burgess–Parr conditions, with an initial hydrogen pressure of 31·5 lb./sq. in., the theoretical volume of hydrogen being absorbed in 1 hour. Fractionation of the product gave 4-2′-*naphthyloctane*, b. p. 116°/0·3 mm., n_D^{20} 1·5559 (Found : C, 90·0; H, 10·1. $C_{18}H_{34}$ requires C, 90·0; H, 10·0%).

In a similar manner, the following 2′-naphthyl derivatives were prepared. 4-2′-*Naphthyldecan*-4-*ol*, from the *n*-propyl ketone and *n*-hexylmagnesium bromide in 85% yield; b. p. 136°/0·4 mm., n_D^{20} 1·5590 (Found : C, 84·7; H, 9·7. $C_{20}H_{34}O$ requires C, 84·5; H, 9·9%). 4-2′-*Naphthyldec*-3- and -4-*ene*, 87% yield, b. p. 150—151°/0·8 mm., n_D^{20} 1·5720 (Found : C, 90·5; H, 9·6. $C_{20}H_{32}$ requires C, 90·2; H, 9·8%). 4-2′-*Naphthyldecane*, 94% yield, b. p. 150°/1 mm., n_D^{20} 1·5457 (Found : C, 89·9; H, 10·3. $C_{20}H_{34}$ requires C, 89·6; H, 10·4%). 4-2′-*Naphthyldodec*-3- and -4-*enes*, 66% overall yield from the *n*-propyl ketone and *n*-octylmagnesium bromide; b. p. 178°/1 mm., n_D^{20} 1·5592 (Found : C, 89·8; H, 10·1. $C_{22}H_{36}$ requires C, 89·8; H, 10·2%). 4-2′-*Naphthyldodecane*, 96% yield, b. p. 183°/1 mm., n_D^{20} 1·5371 (Found : C, 89·4; H, 10·7. $C_{22}H_{38}$ requires C, 89·2; H, 10·8%). 6-2′-*Naphthyldodecan*-6-*ol*, 85% yield from the *n*-pentyl ketone and *n*-hexylmagnesium bromide; b. p. 150°/0·1 mm., n_D^{20} 1·5479 (Found : C, 84·4; H, 10·3. $C_{22}H_{38}O$ requires C, 84·6; H, 10·3%). [The *n*-pentyl ketone was prepared from *n*-hexanoyl chloride in nitrobenzene in 60% yield; in carbon disulphide the yield was only 47%, and the

crude ketone contained an appreciable amount of the 1-isomer (cf. Smith *et al.*, *loc. cit.*).] 6-2′-*Naphthyldodec*-5- and -6-*enes*, 77·6% yield, b. p. 166—168°/1 mm., n_D^{20} 1·5602 (Found: C, 89·8; H, 10·2. $C_{32}H_{30}$ requires C, 89·8; H, 10·2%). 6-2′-*Naphthyldodecane*, 82% yield, b. p. 240—242°/2 mm., n_D^{20} 1·5399 (Found: C, 89·4; H, 10·5. $C_{32}H_{32}$ requires C, 89·2; H, 10·8%). 3-2′-*Naphthyloct*-3- and -4-*enes*, 63% overall yield from the *n*-pentyl ketone and ethylmagnesium chloride; b. p. 170°/1 mm., n_D^{20} 1·5809 (Found: C, 90·9; H, 9·3. $C_{18}H_{22}$ requires C, 90·8; H, 9·2%). 3-2′-*Naphthyloctane*, 92% yield, b. p. 156—157°/1 mm., n_D^{20} 1·5580 (Found: C, 89·9; H, 10·0. $C_{18}H_{24}$ requires C, 90·0; H, 10·0%). None of these branched-chain derivatives could be obtained crystalline.

(C) 1-1′-*Naphthylalkanes*.—n-*Alkyl* 1-*naphthyl ketones*. (*a*) By use of di-1-naphthylcadmium. Di-1-naphthylcadmium was obtained in benzene solution from purified 1-bromonaphthalene (Jones and Lapworth, *loc. cit.*) (30 g.), magnesium (3·5 g.), and dry ether (75 c.c.), dry benzene (75 c.c.) being added to the stirred and heated solution of the Grignard reagent, followed by finely powdered anhydrous cadmium chloride (13·4 g., 1 equiv.). The exchange reaction was complete in about 20 minutes, as determined by Gilman and Schulze's colour reaction (*J. Amer. Chem. Soc.*, 1925, **47**, 2002). The ether was then removed by distillation, and a further quantity (125 c.c.) of dry benzene added. *n*-Octanoyl chloride (19 g., 0·8 mol.) in benzene (60 c.c.) was added in one portion, and stirring and heating were continued for 4 hours. When cool, the product was decomposed with dilute sulphuric acid in the normal way, and the washed and dried benzene extract fractionated. *n-Heptyl* 1-*naphthyl ketone*, b. p. 184°/2 mm., n_D^{20} 1·5661, m. p. −4° to −3°, was obtained in 60% yield (18 g.) by purification on an alumina column, benzene being used as solvent, followed by redistillation (Found: C, 85·0; H, 8·6. $C_{18}H_{22}O$ requires C, 85·1; H, 8·7%). The following ketones were similarly obtained.

1-*Naphthyl* n-*nonyl ketone*, 70% yield, from *n*-decanoyl chloride; m. p. 10° (from chilled acetone), n_D^{20} 1·5570, b. p. 190°/2 mm. (Found: C, 85·1; H, 9·1. $C_{26}H_{44}O$ requires C, 85·1; H, 9·2%). 1-Naphthyl *n*-undecyl ketone, 50% yield, from *n*-dodecanoyl chloride; m. p. 26·8° (thermometer in the melt) [from light petroleum (b. p. 100—120°)], b. p. 234—235°/6 mm., n_D^{20} 1·5430 (Found: C, 85·3; H, 9·4. Calc. for $C_{27}H_{36}O$: C, 85·2; H, 9·7%); Ralston and Christensen (*loc. cit.*) record b. p. 240—245°/5 mm., and Turkiewicz (*loc. cit.*) records $n_D^{25\cdot5}$ 1·5438. *n*-Heptadecyl 1-naphthyl ketone: 40% yield from stearoyl chloride; m. p. 57° [from light petroleum (b. p. 60—80°)] (Found: C, 85·4; H, 10·5. Calc. for $C_{28}H_{42}O$: C, 85·3; H, 10·7%). Seidel and Engelfried (*Ber.*, 1936, **69**, 2567) record m. p. 52—54·5°, Ryan and Nolan (*loc. cit.*), m. p. 53—54°, and Ralston and Christensen (*loc. cit.*) m. p. 53—54°. No ketonic derivatives of these ketones could be prepared.

(*b*) By use of 1-naphthonitrile (cf. Nunn and Henze, *loc. cit.*). The nitrile (30·6 g., 1 mol.) in dry toluene (300 c.c.) was added slowly to a stirred solution of *n*-heptylmagnesium bromide [1 mol., from magnesium (5·0 g.), *n*-heptyl bromide (39·4 g.), and dry ether (250 c.c.)]. The ether was then removed by distillation, more toluene (80 c.c.) being added. After 12 hours' refluxing, the cooled reaction mixture was decomposed by addition of saturated ammonium chloride solution containing chipped ice. The separated aqueous layer was extracted with ether, and the ether and toluene layers were combined. Extraction of this organic solution with 2N-sulphuric acid (3 × 150 c.c.) gave a colourless solution, from which no material could be isolated after 3 hours' heating under reflux. The ether was therefore removed from the ether–toluene extract, and the residual solution heated under reflux for 2 hours with 10N-sulphuric acid (100 c.c.). Removal of the toluene from the washed and dried solution, followed by fractionation of the dark residue, gave a pale yellow oil, b. p. 188°/4 mm. Crystallisation from acetone at −60° gave *n*-heptyl 1-naphthyl ketone (50%), identical with that obtained by method (*a*).

(*c*) By use of 1-bromonaphthalene (cf. Ralston and Christensen, *loc. cit.*; Turkiewicz, *loc. cit.*). 1-Naphthylmagnesium bromide [1 mol.; from purified 1-bromonaphthalene (50·5 g.) and magnesium (5·0 g.)] was stirred and heated under reflux, *n*-octanonitrile (38·3 g., 1 mol.) added slowly, and the heating and stirring continued for a further 6 hours. Decomposition in the normal manner with dilute sulphuric acid yielded an acid layer from which no ketone could be obtained. From the washed and dried ethereal solution, however, *n*-heptyl 1-naphthyl ketone was obtained in 76% yield. The homologous ketones were obtained in a similar manner: *n*-nonyl (70% from *n*-decanonitrile); *n*-undecyl (76% from *n*-dodecanonitrile); and *n*-heptadecyl (80% from stearonitrile).

1-1′-*Naphthylalkanes*. *n*-Heptyl 1-naphthyl ketone (33·8 g.) was placed in a tilting hydrogenator with copper chromite (5 g.) under an initial hydrogen pressure of 100 atm. The temperature was kept at 205° for 3 hours, and the hydrogenator allowed to cool, refilled to 100 atm., and the heating continued for a further 6 hours. After cooling, the product was isolated by means of ether. On distillation, a major fraction collected at 171—174°/6 mm. Redistillation over sodium, followed by crystallisation from acetone at −50°, gave 1-1′-naphthyloctane (25·6 g., 80%), m. p. −2°, b. p. 170°/4 mm., n_D^{20} 1·5510 (Found: C, 90·0; H, 10·1. Calc. for $C_{18}H_{24}$: C, 90·0; H, 10·0%). Luther and Wächter record n_D^{20} 1·55322.

In a similar manner, the following hydrocarbons were obtained: 1-1′-*Naphthyldecane*, 86% yield, m. p. 15° (from acetone at −50°), b. p. 200°/4 mm., n_D^{20} 1·5448 (Found: C, 89·5; H, 10·4. $C_{20}H_{28}$ requires C, 89·6; H, 10·4%). 1-1′-*Naphthyldodecane*, 81·5% yield, needles (from acetone at 0°), m. p. 26·5°, b. p. 209°/4 mm., n_D^{20} 1·5310 (Found: C, 89·0; H, 10·7. $C_{22}H_{32}$ requires C, 89·2; H, 10·8%). 1-1′-*Naphthyloctadecane*, 83% yield, elongated plates (from ethanol), m. p. 53·5°, b. p. 169—171°/0·5 mm. (Found: C, 88·3; H, 11·7. $C_{28}H_{44}$ requires C, 88·4; H, 11·6%); mixed m. p. with 1-2′-naphthyloctadecane 45—47°.

(D) 1 : 6-*Di-2′-naphthylhexane*.—*Polymeric adipic anhydride–tetralin reaction*. Finely powdered anhydrous aluminium chloride (70 g., 1·4 mols.) was added in small portions to a vigorously stirred solution of redistilled tetralin (50 g., 1 mol.) and the polymeric anhydride (27·3 g., 1·1 mols.; prepared by the method of Plant and Tomlinson, *J.*, 1935, 253) in dry, thiophen-free benzene (300 c.c.). After the addition, the mixture was heated under reflux for 3 hours, and the complex decomposed in the normal

manner. The white solid (8 g.) which separated at this stage was adipic acid. The separated benzene layer was washed and dried (Na_2SO_4), the solvent removed at 100°/20 mm., and the unchanged tetralin at 1 mm. The recovered tetralin gave a red precipitate with 2 : 4-dinitrophenylhydrazine. This derivative separated from dioxan as dark red prisms, m. p. 227—228°, and a mixed m. p. with an authentic specimen prepared from 6-acetyltetralin (Scharwin, *Ber.*, 1902, **35**, 2511) showed this to be 6-*acetyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene* 2 : 4-*dinitrophenylhydrazone* (Found : C, 61·2; H, 5·0; N, 15·5. $C_{18}H_{18}O_4N_4$ requires C, 61·0; H, 5·1; N, 15·8%). (When the reaction was carried out with carbon disulphide as solvent, only adipic acid and this derivative could be isolated from the reaction mixture.)

The viscous residue after the removal of the solvent crystallised on trituration with acetone, giving 34 g. of solid. This was shaken in the cold with aqueous sodium carbonate (2N.) for 2 hours, and then filtered. Acidification of the alkaline filtrate with concentrated hydrochloric acid yielded a brown gum, which solidified on stirring. Two crystallisations from benzene yielded slender prisms (18 g.), m. p. 92°. Analysis and degradation showed this to be δ-(5 : 6 : 7 : 8-*tetrahydro*-2-*naphthoyl*)*valeric acid* (Found : C, 73·7; H, 7·6. $C_{16}H_{20}O_3$ requires C, 73·8; H, 7·7%); its 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in deep red prisms, m. p. 144° (Found : N, 12·4. $C_{22}H_{24}O_6N_4$ requires N, 12·7%).

The alkali-insoluble material from the separation was crystallised twice from ethanol, yielding long prismatic needles (12·5 g.), m. p. 91—92° (depressed to 73—75° by admixture with the keto-acid). Analysis and degradation showed this to be 1 : 4-*di*-(5 : 6 : 7 : 8-*tetrahydro*-2-*naphthoyl*)*butane* (Found : C, 83·6; H, 7·8. $C_{26}H_{30}O_2$ requires C, 83·4; H, 8·0%). The *bis*-2 : 4-*dinitrophenylhydrazone* (dark red needles from *cyclo*hexanone) melted at 264° (decomp.) (Found : C, 62·1; H, 5·4. $C_{38}H_{38}O_8N_8$ requires C, 62·1; H, 5·2%).

The diketone was oxidised with selenium dioxide, and the crude product treated with alkaline hydrogen peroxide by the method described under the 2-naphthyl ketones. The resulting tetrahydronaphthoic acid melted at 153° after crystallisation from ethanol (lit., m. p. of 5 : 6 : 7 : 8-tetrahydronaphthalene-2-carboxylic acid, 154°). Dehydrogenation with palladised charcoal at 280° for 4 hours in a stream of hydrogen yielded 2-naphthoic acid. The structure of the keto-acid was proved by degradation to this acid in a similar manner.

1 : 6-*Di*-(5 : 6 : 7 : 8-*tetrahydro*-2-*naphthyl*)*hexane*. The diketone (31·5 g.) was reduced by the normal Huang-Minlon procedure, sodium (14·0 g.), diethylene glycol (360 c.c.), and hydrazine hydrate (40 c.c. of 90%) being used. Distillation of the washed and dried benzene extract yielded a major fraction, b. p. 250—255°/0·5 mm., which was redistilled over sodium. The *hexane* (19·9 g., 69%) crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 47·5° (Found : C, 90·1; H, 9·6. $C_{26}H_{34}$ requires C, 90·2; H, 9·8%).

1 : 6-*Di*-2′-*naphthylhexane*. The ditetralylhexane (15·6 g.) was heated with 10% of its weight of palladised charcoal (Diels and Gädke, *Ber.*, 1925, **58**, 1231) at 260° for 3 hours in a stream of dry, oxygen-free nitrogen. Hydrogen was evolved vigorously at first, and the temperature was raised slowly to 300° for 2 hours whereafter this evolution ceased. The solid obtained on cooling was isolated by extracting it several times with hot benzene. Crystallisation from light petroleum (b. p. 100—120°) gave 1 : 6-*di*-2′-*naphthylhexane* in plates, m. p. 102° (11·7 g., 77%) (Found : C, 92·3; H, 7·5. $C_{26}H_{26}$ requires C, 92·3; H, 7·7%).

A mixture of molecular proportions of the hydrocarbon and picric acid in hot ethanol or benzene yielded a solid, m. p. 96—103°, from which only picric acid could be isolated on attempted purification. However, a solution of the hydrocarbon (0·5 g.) and *s*-trinitrobenzene (0·5 g.) in hot ethanol (20 c.c.) deposited a pale yellow solid on cooling. Crystallisation from the same solvent yielded the trinitrobenzene *complex* in pale yellow needles, m. p. 143—145° (Found : C, 71·2; H, 5·4; N, 7·1. $C_{26}H_{26}.C_6H_3O_6N_3$ requires C, 69·7; H, 5·3; N, 7·6%).

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234. *The Synthesis of Hydrocarbons of High Molecular Weight. Part II. Some Di- and Tri-n-alkylnaphthalenes.*

By B. Bannister and B. B. Elsner.

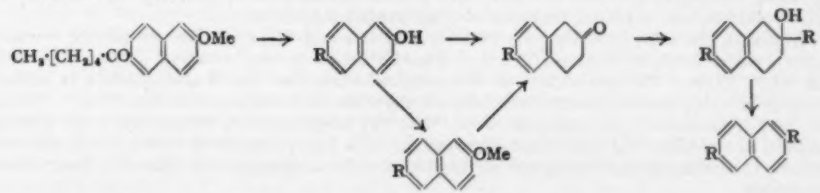
The syntheses of three di-*n*-hexylnaphthalenes and one tri-*n*-butylnaphthalene are described. 2 : 6-Di-*n*-hexylnaphthalene was prepared by the Friedel–Crafts acylation of 2-*n*-hexylnaphthalene, followed by reduction of the 6-*n*-pentyl ketone. Proof of the structure, which could not be obtained by oxidation, was achieved by an unambiguous synthesis from 2-methoxynaphthalene through 6-*n*-hexyl-2-tetralone. Acenaphthenequinone was found to react readily with *n*-pentyl-lithium to give a diol which was oxidised to the 1 : 8-diketone in good yield. Complete reduction catalytically, followed by dehydrogenation, yielded 1 : 8-di-*n*-hexylnaphthalene. 2 : 3-Di-*n*-hexylnaphthalene was obtained from tetralin by the Friedel–Crafts acylation and reduction to the 6-*n*-hexyltetralin. A second hexanoyl group was introduced by the same method and shown to occupy the 7-position by degradation to tetramethyl pyromellitate. Reduction followed by dehydrogenation gave the desired 2 : 3-di-*n*-hexylnaphthalene. A similar series of reactions was used to introduce *n*-butyl groups into the 5-, 6-, and 7-positions of tetralin, and dehydrogenation yielded 1 : 2 : 3-tri-*n*-butylnaphthalene.

(A) *Di-n-Hexylnaphthalenes.*—In continuation of the work reported in Part I (preceding paper), it was considered of interest to synthesise a series of di-*n*-hexylnaphthalenes.

2 : 6-*Di-n-hexylnaphthalene.* Haworth *et al.* (*J.*, 1932, 1784, 2248) have shown in several instances that 2-methylnaphthalene is acylated in the 6-position under Friedel–Crafts conditions in nitrobenzene. This approach to a 2 : 6-derivative was therefore investigated. The Friedel–Crafts reaction with *n*-hexanoyl chloride and 2-*n*-hexylnaphthalene (Bailey, Pickering, and Smith, *J. Inst. Pet.*, 1949, **35**, 103) in nitrobenzene yielded a ketone, characterised as its 2 : 4-dinitrophenylhydrazone and semicarbazone, and later proved to be the expected 6-*n*-hexyl-2-naphthyl *n*-pentyl ketone. Reduction by the Huang-Minlon procedure gave 2 : 6-di-*n*-hexylnaphthalene.

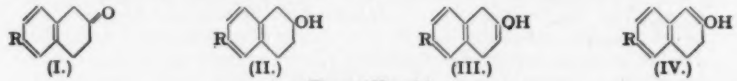
In an attempt to prove the position of the second hexyl group by oxidation to a naphthalenedicarboxylic acid, the hydrocarbon was heated with dilute nitric acid at 190° (cf. Campbell, Soffer, and Steadman, *J. Amer. Chem. Soc.*, 1942, **64**, 425). The product appeared to be a benzenetricarboxylic acid, probably trimellitic acid. This implies that the second hexyl group has entered the other ring, and that the dihexylnaphthalene was symmetrical, *i.e.*, the 2 : 6- or the 2 : 7-compound. As an alternative approach, the oxidation of the ketone in two stages was attempted. Selenium dioxide in boiling dioxan solution gave, after treatment with alkaline hydrogen peroxide (cf. Smith *et al.*, *loc. cit.*), an acid later shown to be 6-*n*-hexyl-2-naphthoic acid. However, further oxidation of this material with dilute nitric acid at 190° resulted in the formation of the same benzenetricarboxylic acid. From attempts to oxidise the hexylnaphthalenecarboxylic acid and the dihexylnaphthalene itself with selenium dioxide at a high temperature (cf. Kacer, D.R.-P. 557,249), only starting material could be isolated.

The investigation of the structure of the dihexylnaphthalene was therefore directed towards an unequivocal synthesis. A method analogous to the synthesis of 2 : 6-dimethylnaphthalene (Royer, *Ann. Chim.*, 1946, **1**, 395; *Compt. rend.*, 1946, **222**, 746) was investigated, as indicated below (R = *n*-hexyl) :



The Friedel–Crafts reaction between 2-methoxynaphthalene and *n*-hexanoyl chloride in nitrobenzene gave a good yield of a ketone, characterised as its 2 : 4-dinitrophenylhydrazone,

oxime, and semicarbazone, and later shown to be 6-methoxy-2-naphthyl *n*-pentyl ketone. An attempt to oxidise this ketone with aqueous sodium hypochlorite was unsuccessful. The selenium dioxide method, however, yielded 6-methoxy-2-naphthoic acid, identical with a specimen obtained by hypochlorite oxidation of the 6-acetyl compound (Haworth and Sheldrick, *J.*, 1934, 864). Reduction of the ketone by the Huang-Minlon method was accompanied by complete demethylation, the product being 6-*n*-hexyl-2-naphthol. Since the phenol was produced, reduction to the β-tetralone was attempted by Birch's method (*J.*, 1944, 430) with sodium in liquid ammonia, ethanol being used as the proton source. From the bisulphite extract of the product, a colourless oil was obtained, shown by analysis to be 6-*n*-hexyl-2-tetralone (I). The non-ketonic residue from the bisulphite extraction contained no unchanged naphthol, and was distilled, yielding as major fraction a colourless oil, a colourless solid also being obtained but in too small a quantity for investigation. The oil was indicated by analysis and insolubility in alkali to be 6-*n*-hexyl-1 : 2 : 3 : 4-tetrahydro-2-naphthol (II). The intermediate in the reduction of the naphthol is considered to be the unconjugated dihydronaphthol (III), which, in the presence of the alkali, isomerises to the conjugated form (IV), which undergoes further reduction to the tetrahydro-stage.



(I.) (II.) (III.) (IV.)

(R = *n*-Hexyl.)

Since the sodium–liquid ammonia reduction gave unsatisfactory results, the naphthol was methylated, and reduction of the hexylmethoxynaphthalene was carried out by Rowe and Levin's method (*J.*, 1921, 119, 2021), xylene being used as inert solvent and ethanol as the proton source. The reduction product, a colourless oil, gave analytical data in agreement with a dihydro-derivative, and was considered to be the unconjugated 6-*n*-hexyl-1 : 4-dihydro-2-methoxynaphthalene. After hydrolysis of the enol ether, the bisulphite derivative yielded the 6-*n*-hexyl-2-tetralone (I) in 53% yield, of the same refractive index as that obtained from the sodium–liquid ammonia reduction. From the bisulphite extraction, a colourless, non-ketonic oily residue was obtained, and was indicated by analysis and reactions to be a dihydro-derivative of the hexyl-substituted ring. It is considered to be 6-*n*-hexyl-5 : 8-dihydro-2-methoxynaphthalene. The reduction product which gave analytical data consistent with the enol ether is therefore shown to be a mixture of this material and the 5 : 8-dihydro-compound.

The product of the Grignard reaction of *n*-hexylmagnesium bromide with the β-tetralone could not be purified, and the impure 2 : 6-di-*n*-hexyl-1 : 2 : 3 : 4-tetrahydro-2-naphthol was dehydrated and dehydrogenated in one stage by use of a highly active palladium–charcoal catalyst (Zelinsky and Turowa-Pollak, *Ber.*, 1925, 58, 1295). The melting point of the product was undepressed on admixture with the di-*n*-hexylnaphthalene obtained from 2-*n*-hexylnaphthalene, thus proving the second hexyl group to occupy the 6-position. The identity of the two dihexylnaphthalenes orients also the hexanoylhexylnaphthalene and the hexylnaphthoic acid.

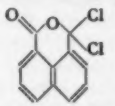
1 : 8-*Di*-n-*Hexylnaphthalene*. Although the problem of the synthesis of 1 : 8-dialkylnaphthalenes has attracted the attention of several workers, the only compound of this type which has been prepared is the 1 : 8-dimethyl derivative. Naphthalene-1 : 8-dicarboxylic anhydride (naphthalic anhydride) appeared to be a suitable starting material, having substituents in the required positions. The reaction between di-*n*-pentylcadmium and the anhydride, however, yielded a red gum, and only unchanged anhydride could be recovered. By using *n*-pentylmagnesium bromide, only a small quantity of acidic material, which could not be purified, was obtained, together with unchanged anhydride.

Although the anhydride shows a marked lack of reactivity, and fails completely to react under Friedel–Crafts conditions, yet the di-acid chloride is very reactive (Mason, *J.*, 1924, 125, 2116, 2119). The interaction of di-*n*-penylcadmium and the di-acid chloride in boiling benzene led to an almost quantitative yield of anhydride after decomposition, however. Mason (*loc. cit.*) suggested the unsymmetrical rather than the unsymmetrical structure for the di-acid chloride, as a result of the ready diester formation. The lack of reactivity of the di-acid chloride towards the cadmium alkyl suggests the existence of the unsymmetrical form (V) under these conditions.

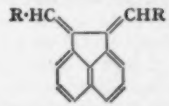
The next starting material investigated was acenaphthenequinone. By condensation of alkylmagnesium bromides with this substance, Maxim (*Bull. Soc. chim.*, 1928, 43, 769; 1929,

45, 1137) prepared a series of 7 : 8-dialkylacenaphthene-7 : 8-diols, the yield of which decreased from 70% for the dimethyl to 30% for the di*iso*amyl compound, a large amount of unchanged quinone being recovered from the reaction with the longer-chain alkylmagnesium bromides.

In a repetition of Maxim's work on the formation of the di-*n*-propyl-diol, for which he does not record a yield, it was found that only a 9% yield could be obtained, together with 60% of unchanged quinone, and a small amount of a viscous red oil. The reaction between *n*-pentylmagnesium bromide and acenaphthenequinone was carried out by Maxim's procedure. A deep



(V.)



(VI.)

red colour rapidly developed, and decomposition of the reaction mixture led to the recovery of much unchanged quinone, together with a viscous deep red oil, which was unsaturated, and from which no pure material could be isolated. However, the red oil is considered to be impure 7 : 8-di-*n*-pentylideneacenaphthene (VI; R = CH_3·$[CH_2]_3$·), formed by dehydration *in situ* of the 7 : 8-di-*n*-pentyl-diol. Maxim records the formation, by the dehydration of the diols with mineral acid, of red oils which appear to be dienes of this type (see also Campbell and Gow, *J.*, 1949, 1555). The condensation of straight-chain alkylmagnesium bromides with acenaphthenequinone is therefore of little use with homologues above ethyl.

Wittig *et al.* (see, *e.g.*, Wittig, "Newer Methods of Preparative Organic Chemistry," 1948 edn., p. 521; Wicks, *Interchem. Rev.*, 1946, **6**, 69) have found that, although certain diketones give glycols in poor yield, or not at all, with organomagnesium compounds, yet organolithium derivatives give excellent yields of the glycols. The interaction of *n*-pentyl-lithium and acenaphthenequinone proved to be successful. On the addition of the solid quinone to the ethereal pentyl-lithium solution, a vigorous reaction developed. The colourless solid, obtained after decomposition, was shown by analysis and reactions to be the required 7 : 8-di-*n*-pentylacenaphthene-7 : 8-diol. No isomeric diol could be obtained from the reaction mixture, but a small quantity of a red oil was obtained from the ethereal mother-liquors of the dipentyl-diol. No purification of this material could be effected, but from its colour and rapid decolorisation of aqueous potassium permanganate, it is considered to be the impure dipentylideneacenaphthene (VI), also formed as the sole product isolated from the corresponding Grignard reaction. The failure to form an adduct of this compound with maleic anhydride is probably due to the steric hindrance of the pentylidene groups (see Campbell and Gow, *loc. cit.*).

The glycol fission was achieved by the use of lead tetra-acetate. The oxidation gave only a 34% yield of 1 : 8-di-*n*-hexanoylnaphthalene when carried out in glacial acetic acid, much unchanged diol being recovered. In benzene solution, however, the yield of pure diketone was 80%. A solution of the diketone gave a red colour with 2 : 4-dinitrophenylhydrazine sulphate, but no solid derivative could be isolated. Similarly, no conversion into the perinaphthinden-1-one could be achieved with piperidine as catalyst (cf. Criegee *et al.*, *Annalen*, 1933, **507**, 176). In view of our inability (see Part I) to obtain derivatives of the *n*-alkyl 1-naphthyl ketones, it is not surprising that the 1 : 8-diketone is also unreactive. The presence of the carbonyl groups in the molecule was proved by the infra-red spectrum, which showed a strong absorption band at 1685 ν.

As with the *n*-alkyl 1-naphthyl ketones, this lack of reactivity again gave rise to the problem of the conversion of the carbonyl into methylene groups. Hydrogenation under high temperature and pressure with copper chromite as catalyst, successful in the former case, gave a product containing oxygen, and with a high percentage of hydrogen, suggesting the partial reduction of the naphthalene nucleus. A similar result was obtained by using Hartung's palladium–charcoal catalyst with a glacial acetic acid solution of the ketone at 80° under 3 atm. (cf. Hornung and Reisner, *J. Amer. Chem. Soc.*, 1949, **71**, 1870; Ju, Shen, and Wood, *J. Inst. Petrol.*, 1940, **26**, 514). Since it seemed to be impossible to reduce the diketone without causing partial reduction of the nucleus simultaneously, it was decided to hydrogenate the molecule by using Raney nickel as catalyst at a high temperature and pressure. Repeated treatment yielded 1 : 8-di-*n*-hexyldecahydronaphthalene. Dehydrogenation of the latter, by the aid of a highly active palladium–charcoal catalyst, was accomplished in moderate yield, giving 1 : 8-di-*n*-hexylnaphthalene.

2 : 3-*Di*-n-*hexylnaphthalene*. The best route to certain di- and poly-alkylnaphthalenes, in which the substituents are in the same ring, starts from tetralin (cf. Scharwin, *Ber.*, 1902, **35**,

2511; Fleischer and Siefert, *Ber.*, 1920, **53**, 1255; Smith and Lo, *J. Amer. Chem. Soc.*, 1948, **70**, 2209). *n*-Pentyl 5 : 6 : 7 : 8-tetrahydro-2-naphthyl ketone was prepared by the Friedel–Crafts reaction, *n*-hexanoyl chloride being used in nitrobenzene solution. Reduction to the 6-*n*-hexyltetralin was achieved by means of both the Huang-Minlon method, and catalytically, by means of copper chromite. Re-acylation of this hydrocarbon with *n*-hexanoyl chloride gave a ketone, subsequently shown to be 3-*n*-hexyl-5 : 6 : 7 : 8-tetrahydro-2-naphthyl *n*-pentyl ketone, although no ketonic derivatives could be obtained. The positions of the substituents were proved by oxidation with dilute nitric acid at 190° (cf. Smith and Lo, *loc. cit.*). The solid product obtained from the aqueous solution was methylated with diazomethane, and a mixed m. p. with an authentic specimen showed it to be tetramethyl pyromellitate. The ketone was reduced by means of high temperature and pressure hydrogenation in the presence of copper chromite, and the 6 : 7-di-*n*-hexyltetralin dehydrogenated in good yield over a palladium–charcoal catalyst to 2 : 3-di-*n*-hexylnaphthalene. After the completion of this work, both 6-*n*-hexyl- and 6 : 7-di-*n*-hexyl-tetralins were reported by Hart and his co-workers (*J. Amer. Chem. Soc.*, 1948, **70**, 3731; 1950, **72**, 1249). The refractive indices they record agree with ours.

(B) 1 : 2 : 3-*Tri*-n-*butylnaphthalene*.—In order to obtain a trisubstituted naphthalene of the same molecular weight, the corresponding series of reactions was used to introduce *n*-butyl groups. *n*-Propyl 5 : 6 : 7 : 8-tetrahydro-2-naphthyl ketone was obtained in good yield by Barbot's method (*Bull. Soc. chim.*, 1930, **47**, 1314). The Huang-Minlon reduction, followed by re-acylation, gave 3-*n*-butyl-5 : 6 : 7 : 8-tetrahydro-2-naphthyl *n*-propyl ketone, the structure of which was proved by the method employed for the hexanoylhexyltetralin above. Clemmensen and catalytic reduction, with copper chromite, afforded the 6 : 7-di-*n*-butyltetralin in good yield, and of refractive index in agreement with that later recorded by Hart *et al.* (*loc. cit.*). The Friedel–Crafts reaction with *n*-butyryl chloride in carbon disulphide solution gave a moderate yield of a ketone, which must be the 5-derivative, since the 5- and the 8-position in the dibutyltetralin are equivalent. No ketonic derivatives of this ketone could be prepared. The high temperature and pressure reduction of this material using copper chromite gave the 5 : 6 : 7-tri-*n*-butyltetralin together with some unchanged ketone. More drastic conditions gave the 1 : 2 : 3-tri-*n*-butyldecalin. The tetralin was dehydrogenated to 1 : 2 : 3-tri-*n*-butylnaphthalene as in the previous case.

Experimental.

2 : 6-*Di*-n-*hexylnaphthalene*.—6-n-*Hexyl*-2-*naphthyl* n-*pentyl ketone*. 2-*n*-Hexylnaphthalene was prepared by the method of Smith *et al.* (*loc. cit.*). The *n*-hexyl chain was shown to be unaffected by anhydrous aluminium chloride under Friedel–Crafts conditions by recovering unchanged material from a solution of the two in nitrobenzene. The hydrocarbon (53 g., 1 mol.) in dry nitrobenzene (200 c.c.) containing *n*-hexanoyl chloride (40 g., 1·2 mols.) was treated with anhydrous aluminium chloride (40 g., 1·2 mols.) in the cold, and the product isolated in the normal manner (see preceding paper). The crude material, b. p. 255—257°/12 mm., crystallised from ethanol in plates (56 g., 72%), m. p. 55°, later shown to be 6-n-*hexyl*-2-*naphthyl* n-*pentyl ketone* (Found: C, 85·2; H, 9·6. $C_{23}H_{36}O$ requires C, 85·2; H, 9·7%). The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in elongated orange prisms, m. p. 159° (Found: C, 69·0; H, 6·9; N, 11·6. $C_{29}H_{40}O_4N_4$ requires C, 68·6; H, 6·9; N, 11·4%), and the *semicarbazone* from ethanol in plates, m. p. 142° (Found: C, 75·1; H, 9·0; N, 11·0. $C_{24}H_{39}ON_3$ requires C, 75·2; H, 9·0; N, 11·4%).

2 : 6-*Di*-n-*hexylnaphthalene*. The ketone (30 g.) was reduced by the normal Huang-Minlon procedure, sodium (7·5 g.) in diethylene glycol (180 c.c.), and hydrazine hydrate (20 c.c.; 90%) being used. Isolation of the product with benzene gave a colourless oil, b. p. 207—208°/1 mm. Crystallisation from ethanol at 0° gave 2 : 6-*di*-n-*hexylnaphthalene* in prisms, m. p. 36·5—37° (Found: C, 89·1; H, 10·9. $C_{22}H_{36}$ requires C, 89·2; H, 10·8%).

Oxidation of 2 : 6-*di*-n-*hexylnaphthalene*. The hydrocarbon (0·1 g.) was heated in a sealed tube at 190° for 20 hours with nitric acid (1·8 c.c.; *d* 1·42) and water (3·6 c.c.). Evaporation of the solution from three such oxidations gave a colourless solid (0·2 g.), m. p. 210—215°, which crystallised from water in needles, m. p. 214—216°. The analysis agrees with that of a benzenetricarboxylic acid (Found: C, 51·1; H, 3·1. Calc. for $C_9H_6O_6$: C, 51·4; H, 2·9%). A suspension of the acid in ether was treated with ethereal diazomethane. Removal of the solvent gave an oil which could not be obtained crystalline (trimellitic acid has m. p. 216°; its trimethyl ester, m. p. −13°).

Oxidation of 6-n-*hexyl*-2-*naphthyl* n-*pentyl ketone*. The ketone (5·0 g.) was oxidised with selenium dioxide (4·2 g.) in boiling dioxan (50 c.c.), and the crude product treated with alkaline hydrogen peroxide. Crystallisation of the acidic product from light petroleum (b. p. 80—100°) and then from acetic acid yielded prisms (0·6 g.; m. p. 141°) of a substance later shown to be 6-n-*hexyl*-2-*naphthoic acid* (Found: C, 79·5; H, 7·6. $C_{17}H_{26}O_2$ requires C, 79·7; H, 7·8%). Further oxidation of this acid with dilute nitric acid at 190° resulted in formation of the benzenetricarboxylic acid described above.

From attempts to oxidise the hexylnaphthalenecarboxylic acid and the dihexylnaphthalene with selenium dioxide in boiling nitrobenzene, only unchanged material could be isolated.

6-*Methoxy*-2-*naphthyl* n-*pentyl ketone*. 2-Methoxynaphthalene (79·0 g., 1 mol.) and *n*-hexanoyl chloride (81·0 g., 1·2 mols.) in dry nitrobenzene (320 c.c.) were treated at 0° with anhydrous aluminium chloride (87·0 g., 1·3 mols.). Isolation of the product in the usual manner gave the crude material, b. p. 203—205°/1·9 mm. Crystallisation from light petroleum (b. p. 40—60°) gave 78·9 g. (62%) of a substance later shown to be 6-*methoxy*-2-*naphthyl* n-*pentyl ketone* as plates, m. p. 65° (Found: C, 79·9; H, 7·8. $C_{17}H_{20}O_2$ requires C, 79·7; H, 7·8%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate as dark red needles, m. p. 195° (Found: N, 12·9. $C_{23}H_{24}O_5N_4$ requires N, 12·8%). From ethanol, the *semicarbazone* crystallised in prisms, m. p. 174° (Found: N, 13·4. $C_{18}H_{23}O_2N_3$ requires N, 13·4%), and the *oxime* in needles, m. p. 100° (Found: C, 75·4; H, 7·9. $C_{17}H_{21}O_2N$ requires C, 75·3; H, 7·8%).

Oxidation of 6-*methoxy*-2-*naphthyl* n-*pentyl ketone*. No acidic material could be isolated from the attempted oxidation of the ketone by heating with aqueous sodium hypochlorite for 8 hours. However, from the ketone (3·0 g.) and selenium dioxide (2·6 g.) in boiling dioxan (50 c.c.) for 8 hours, followed by treatment with alkaline hydrogen peroxide, an acid was isolated, which separated from ethanol in needles, m. p. 197—198°, after purification by heating the alcoholic solution with kieselguhr. No depression resulted on admixture with an authentic specimen of 6-methoxy-2-naphthoic acid prepared by the alkaline hypochlorite oxidation of 6-methoxy-2-naphthyl methyl ketone (Haworth and Sheldrick, *J.*, 1934, 864).

6-n-*Hexyl*-2-*naphthol*. The methoxynaphthyl ketone (30·0 g.) was reduced by the usual Huang) Minlon procedure, sodium (7·5 g.), diethylene glycol (210 c.c.), and hydrazine hydrate (15 c.c.; 90%) being used. After 9 hours at 220°, the red upper layer of hydrazone had completely disappeared. Benzene extraction of the cooled and diluted reaction mixture failed to yield a product, showing that complete hydrolysis of the methoxyl group had occurred. From the benzene extract of the solution after acidification with hydrochloric acid, a yellow oil was obtained, which solidified on cooling. Two crystallisations from light petroleum (b. p. 80—100°) yielded 6-n-*hexyl*-2-*naphthol* in large plates, m. p. 101° (20·3 g., 76%) (Found: C, 84·3; H, 8·9. $C_{16}H_{24}O$ requires C, 84·2; H, 8·8%). The *phenylurethane*, prepared by heating the naphthol and phenyl *iso*cyanate on the water-bath for 3 hours, separated from light petroleum (b. p. 100—120°) in plates, m. p. 135—136° (Found: C, 79·7; H, 7·3; N, 4·4. $C_{23}H_{25}O_2N$ requires C, 79·5; H, 7·2; N, 4·0%).

Reduction of 6-n-*hexyl*-2-*naphthol*. A solution of the naphthol (4·0 g., 1 mol.) in ethanol (4·1 c.c., 2 mols.) was added cautiously to liquid ammonia (200 c.c.). To the stirred solution, sodium (1·8 g., 2·2 atoms) was added slowly. At the end of the addition, the ammonia was allowed to evaporate, and water (100 c.c.) added to the white residue. The resultant gummy blue material was rapidly acidified with concentrated hydrochloric acid, and the oil extracted with ether. Removal of the solvent from the washed and dried solution gave a red oil, which was shaken for 4 hours with a saturated aqueous solution of sodium hydrogen sulphite. The microcrystalline bisulphite compound was then removed at the pump, washed with ether, and decomposed by warming it for ½ hour on the water-bath with dilute hydrochloric acid. The oil which separated was isolated by means of ether, and distilled in a bulb apparatus. A colourless oil (1·0 g.) distilled at 184—185° (bath-temp.)/1 mm., and redistilled at 187°/1 mm. This compound, m. p. −2° to −1°, n_D^{20} 1·5249, was shown to be 6-n-*hexyl*-2-*tetralone*. The pure ketone was obtained in 20% yield (0·8 g.) (Found: C, 83·7; H, 9·5. $C_{16}H_{22}O$ requires C, 83·5; H, 9·6%). No crystalline derivatives of this ketone could be obtained with 2 : 4-dinitrophenylhydrazine sulphate, semicarbazide hydrochloride, or 4-phenylsemicarbazide. A solution in ethanol gave the characteristic " tetralone blue " colour with aqueous alkali, however.

The ethereal solution of the non-ketonic reduction product was extracted with alkali, but no phenolic material was present. Removal of the solvent gave a red oil, from which two fractions were collected on bulb distillation: (i) a pale yellow oil, b. p. 200°/1·6 mm., and (ii) a colourless oil, b. p. 205°/1·6 mm., which solidified on cooling. The first fraction was redistilled, b. p. 185—187°/1 mm., and is considered to be 6-n-*hexyl*-1 : 2 : 3 : 4-*tetrahydro*-2-*naphthol* (1·0 g., 25%) (Found: C, 82·7; H, 10·0. $C_{16}H_{24}O$ requires C, 82·8; H, 10·3%). The solid (0·5 g.) was shown to be non-ketonic: repeated crystallisation gave needles, m. p. 80—87°, and no further purification could be effected.

Reduction of 6-n-*hexyl*-2-*methoxynaphthalene*. The hexylnaphthol was methylated in 74% yield by using methyl sulphate and 66% aqueous potassium hydroxide in acetone. 6-n-*Hexyl*-2-*methoxynaphthalene* crystallised from ethanol in plates, m. p. 56° (Found: C, 84·5; H, 9·3. $C_{17}H_{26}O$ requires C, 84·3; H, 9·1%). A solution of the methoxy-compound (20·0 g., 1 mol.) in dry xylene (350 c.c.) containing sodium (9·5 g., 2·5 equivs.) was heated to boiling and stirred vigorously. Dry ethanol (24 c.c., 2·5 equivs.) was then added through the condenser as rapidly as possible. At the end of the reaction, ethanol (2·5 c.c.) was added to remove any sodium, and the reaction mixture cooled. Water (400 c.c.) was then added, and the xylene layer removed. Fractionation of the washed and dried solution gave a colourless mobile oil, b. p. 168—171°/1 mm., n_D^{20} 1·5416. The oil gave a 2 : 4-dinitrophenylhydrazone colour reaction, and a " tetralone blue " colour after treatment with mineral acid, and appeared to be 6-*n*-hexyl-1 : 4-dihydro-2-methoxynaphthalene (Found: C, 83·6; H, 10·0. $C_{17}H_{24}O$ requires C, 83·6; H, 9·8%).

The oil (18·5 g.) was dissolved in ethanol (250 c.c.) containing aqueous hydrochloric acid (50 c.c.; 10%), and warmed on the water-bath for 20 minutes. A pale red oil was isolated by means of ether, and was shaken with saturated sodium hydrogen sulphite solution. The bisulphite compound was decomposed as described above, and purification of the product gave the hexyl-β-tetralone in 53% yield (9·2 g.), identical with the material obtained from the hexylnaphthol.

From the ethereal washings of the bisulphite compound, an oil was isolated, which distilled at 169—170°/1 mm., n_D^{20} 1·5359 (4·9 g., 24%); it was non-ketonic, and is considered to be 6-n-*hexyl*-5 : 8-*dihydro*-2-*methoxynaphthalene* (Found: C, 83·6; H, 9·8. $C_{17}H_{24}O$ requires C, 83·6; H, 9·8%).

2 : 6-*Di*-n-*hexylnaphthalene*. The tetralone (6·0 g., 1 mol.) was added in ether to an excess of *n*-hexylmagnesium bromide at room temperature, and the reaction mixture then heated under reflux for 12 hours. Decomposition and isolation of the product in the normal manner, followed by distillation, gave a fore-run of ketone, and the b. p. then rose steadily from 158° to 179°/0·1 mm. This crude carbinol (1·7 g.) was heated at 240° with a palladium–charcoal catalyst (0·2 g.; 30%) (Zelinsky and Turowa-Pollak, *Ber.*, 1925, **58**, 1295), with a slow stream of carbon dioxide passing over the surface. A vigorous reaction occurred in the first few minutes, after which the temperature was raised to 260° for 1½ hours, and finally to 300° for 10 minutes. The product was isolated with the aid of acetone: distillation gave a colourless oil, b. p. 200—230°/1·4 mm., which crystallised on cooling. Recrystallisation from chilled ethanol gave 2 : 6-di-*n*-hexylnaphthalene, colourless plates, m. p. 36°, undepressed on admixture with the hydrocarbon obtained from 2-*n*-hexylnaphthalene.

1 : 8-*Di*-n-*hexylnaphthalene*. The reactions of naphthalene-1 : 8-dicarboxylic anhydride (Graebe and Gfeller, *Ber.*, 1892, **25**, 653) with di-*n*-pentylcadmium and with *n*-pentylmagnesium bromide, and of the dicarboxyl dichloride with di-*n*-pentylcadmium proved useless for the present investigation (see p. 1062).

Reactions of Acenaphthenequinone.—*n*-Pentylmagnesium bromide (1 mol.; from *n*-pentyl bromide, 16·6 g.) was stirred vigorously at room temperature, and finely powdered acenaphthenequinone (5 g., 0·5 mol.) was added slowly. The solution rapidly became deep red, and heat was evolved. The mixture was then heated under reflux for 4 hours, kept overnight, and worked up by Maxim's general method (*loc. cit.*). Unchanged quinone (2·3 g.) was recovered from the orange ethereal solution, which, on removal of solvent, gave a deep red oil, from which no pure material could be isolated, but which reacted rapidly with cold aqueous permanganate. This oil is probably impure 7 : 8-di-*n*-pentylideneacenaphthene. A modification using an excess of Grignard reagent, and the temperature being kept at 0° throughout the reaction, gave an 82% recovery of quinone, together with a small quantity of the red oil. A repetition of the reaction with *n*-propylmagnesium bromide (Maxim, *loc. cit.*) gave a 9% yield of the di-*n*-propyl-diol, m. p. 171° (Maxim, m. p. 173°), together with much unchanged quinone and an unsaturated red oil.

7 : 8-*Di*-n-*pentylacenaphthene*-7 : 8-*diol*. Lithium metal (25·0 g., 2·2 atoms) was hammered under liquid paraffin into thin foil, which was cut into strips and dropped through a rapid stream of dry, oxygen-free nitrogen into dry ether (700 c.c.). *n*-Pentyl chloride (174 g., 1 mol.) in dry ether (300 c.c.) was added until reaction began; stirring was then commenced, and the addition regulated so as to maintain gentle reflux, the nitrogen stream being continued. The mixture was then heated under reflux for 2 hours. After cooling, the ethereal pentyl-lithium was transferred to a second flask under nitrogen pressure, being filtered from unchanged lithium and the bulk of lithium chloride by passing it through an inverted filter funnel covered with fine muslin. The residual solid was washed three times with ether, and the combined ethereal solutions were cooled in an efficient freezing mixture and stirred under nitrogen. Acenaphthenequinone (50·0 g., 0·5 mol.) was finely powdered and added in small portions to this solution. A vigorous reaction resulted, and the solution developed a red-purple colour. After the addition, the mixture was stirred at room temperature for 2 hours. Next day, the lithium complex was decomposed by careful addition of water to the stirred and cooled solution. The white solid (20·9 g.; m. p. 148—150°) which separated at this stage was removed at the pump and washed with ether. The combined ethereal solutions, after being washed and dried ($MgSO_4$), gave a light brown solid on removal of the solvent. Trituration with light petroleum (b. p. 40—60°) gave a white solid (45·1 g.; m. p. 147—148°, undepressed on admixture with that obtained above). The combined solids were crystallised from benzene and then light petroleum (b. p. 100—120°), giving 7 : 8-*di*-n-*pentylacenaphthene*-7 : 8-*diol* (58·0 g., 65%) as needles, m. p. 150° (Found: C, 80·9; H, 9·2. $C_{22}H_{30}O_2$ requires C, 81·0; H, 9·2%).

From the light petroleum washings of the crude diol, a viscous red oil (15·7 g.) was obtained. Although no pure material could be isolated, it reacted rapidly with aqueous permanganate, and appeared to be the impure di-*n*-pentylideneacenaphthene.

1 : 8-*Di*-n-*hexanoylnaphthalene*. The diol (16·8 g., 1 mol.) in dry benzene (400 c.c.) was shaken at room temperature with lead tetra-acetate (23 g., 1 mol.) for 4 hours, then warmed on the water-bath for ½ hour, and poured into a large volume of water. Removal of the solvent from the washed and dried benzene layer yielded a colourless oil, which solidified on cooling. Crystallisation from benzene gave plates, m. p. 86·0—86·5° (13·4 g., 80%) (Found: C, 81·3; H, 8·4. $C_{22}H_{34}O_2$ requires C, 81·5; H, 8·6%). When the reaction was carried out in glacial acetic acid, *ca.* 30% of unchanged diol was recovered. The crude diketone could only be purified by adsorption on alumina and elution with light petroleum (b. p. 60—80°). The pure diketone was obtained in 34% yield.

A solution of the diketone in methanol gave a red colour with 2 : 4-dinitrophenylhydrazine sulphate, but no solid derivative could be obtained. Also, no perinaphthindenone could be obtained by heating the diketone in piperidine solution. The strong infra-red absorption band at 1685 ν proved the presence of the carbonyl group, however.

1 : 8-*Di*-n-*hexyldecahydronaphthalene*. Copper chromite being used as catalyst, and with high temperature and pressure, hydrogenation of the diketone yielded a material shown by analysis to contain oxygen and too high a percentage of hydrogen for a naphthalene derivative. Similar results were obtained by using Hartung's palladised charcoal in acetic acid at 65° (cf. Hornung and Reisner, *loc. cit.*; Ju, Shen, and Wood, *loc. cit.*).

The diketone (18·5 g.) was hydrogenated with Raney nickel in the absence of solvent under an initial hydrogen pressure of 120 atm. The temperature was raised to 250°, and kept thereat for 4 hours. After cooling, additional catalyst was added, and the hydrogenation continued. After a repetition with a third amount of catalyst, the product was isolated by means of ether, and distillation, followed by

redistillation over sodium, gave 1 : 8-*di*-n-*hexyldecahydronaphthalene*, b. p. 160—162°/1 mm., n_D^{20} 1·4783 (14·3 g., 80%) (Found : C, 86·3; H, 13·4. $C_{22}H_{42}$ requires C, 86·3; H, 13·7%).

1 : 8-*Di*-n-*hexylnaphthalene*. The dihexyldecalin (11·5 g.) was heated with 30% palladised charcoal in a metal-bath at 310° for 5 hours under a stream of nitrogen, vigorous hydrogen evolution occurring initially. The temperature was then raised to 330°, and kept thereat for an additional 2 hours. Isolation by means of ether gave an oil, b. p. 170—175°/3 mm. From its refractive index (1·5163) it appeared to be a tetrahydro-derivative, and so was dehydrogenated again as before. Isolation with ether followed by fractionation gave 1 : 8-*di*-n-*hexylnaphthalene*, b. p. 198—200°/3 mm., n_D^{20} 1·5531, m. p. −9° to −8° (Found : C, 89·0; H, 11·0. $C_{22}H_{38}$ requires C, 89·2; H, 10·8%).

2 : 3-*Di*-n-*hexylnaphthalene*.—n-*Pentyl* 5 : 6 : 7 : 8-*tetrahydro*-2-*naphthyl ketone*. The Friedel–Crafts reaction was conducted in the normal manner, tetralin (132 g., 1 mol.), *n*-hexanoyl chloride (148 g., 1·1 mols.), and aluminium chloride (148 g., 1·1 mols.) being used in dry nitrobenzene (540 c.c.) at 0°. The *ketone* was obtained as a colourless oil (153·6 g., 67%), b. p. 198—199°/13 mm., n_D^{20} 1·5366, m. p. 3° (Found : C, 83·8; H, 9·6. $C_{16}H_{22}O$ requires C, 83·5; H, 9·6%). Its 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in dark red needles, m. p. 170° (Found : C, 64·6; H, 6·4. $C_{22}H_{26}O_4N_4$ requires C, 64·4; H, 6·3%), and its *semicarbazone* crystallised from ethanol in prisms, m. p. 159° (Found : C, 71·3; H, 8·7. $C_{17}H_{25}ON_3$ requires C, 71·1; H, 8·7%).

6-n-*Hexyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*. The ketone (60 g.) in diethylene glycol (350 c.c.), containing sodium (15 g.) and hydrazine hydrate (30 c.c.; 90%), was treated under the normal Huang-Minlon conditions. Redistillation of the crude product, isolated by means of benzene, gave 6-*n*-hexyl-1 : 2 : 3 : 4-tetrahydronaphthalene (48·3 g., 86%) as a colourless oil, b. p. 160°/10 mm., n_D^{20} 1·5182 (Found : C, 88·6; H, 11·2. Calc. for $C_{16}H_{24}$: C, 88·9; H, 11·1%). Catalytic reduction by means of copper chromite at 210° and an initial hydrogen pressure of 80 atm. gave the same product in 82% yield. Hart *et al.* (*loc. cit.*) report n_D^{20} 1·5177.

3-n-*Hexyl*-5 : 6 : 7 : 8-*tetrahydro*-2-*naphthyl* n-*pentyl ketone*. As with 2-*n*-hexylnaphthalene, the side chain was shown to be unaffected by aluminium chloride. The 6-*n*-hexyltetralin (77·8 g.) was acylated under the normal conditions, *n*-hexanoyl chloride (53·5 g.), anhydrous aluminium chloride (53·0 g.), and nitrobenzene (200 c.c.) being used. Purification of the crude product yielded the *ketone* as a colourless oil (84 g., 74%), b. p. 198—200°/2·5 mm., n_D^{20} 1·5196 (Found : C, 83·9; H, 11·0. $C_{22}H_{34}O$ requires C, 84·1; H, 10·8%). No solid derivatives of this ketone could be obtained.

Following the method of Smith and Lo (*loc. cit.*), the ketone (4 drops) was heated with nitric acid (1·8 c.c.; *d* 1·42) and water (3·6 c.c.) at 190—200° for 20 hours. The colourless solid (0·2 g.) obtained on evaporation of three such oxidations was suspended in ether and esterified with diazomethane (from 2·0 g. of *N*-nitrosomethylurea). Two crystallisations from methanol yielded plates, m. p. 141°, undepressed on admixture with tetramethyl pyromellitate.

6 : 7-*Di*-n-*hexyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*. The ketone (38·4 g.) was hydrogenated under an initial hydrogen pressure of 195 atm. by using copper chromite as catalyst and a final temperature of 195° for 6 hours. Isolation by means of ether gave the product as a colourless oil (28·2 g., 77%), b. p. 191—192°/4 mm., n_D^{20} 1·5090, m. p. 4—5°. Clemmensen reduction gave the same material in 54% yield (Found : C, 88·1; H, 11·8. Calc. for $C_{22}H_{38}$: C, 88·0; H, 12·0%). Hart *et al.* (*loc. cit.*) report n_D^{20} 1·5090 for this hydrocarbon.

2 : 3-*Di*-n-*hexylnaphthalene*. The dihexyltetralin (20·6 g.) was heated with 10% of its weight of 10% palladised charcoal (Diels and Gädke, *Ber.*, 1925, **58**, 1231) at 260° for 3 hours in a stream of nitrogen. The evolution of hydrogen was vigorous at first. The temperature was then raised slowly at 300° and kept thereat until the evolution of hydrogen ceased (*ca.* 2 hours). Isolation of the product with the aid of ether gave 2 : 3-*di*-n-*hexylnaphthalene* as a colourless oil, m. p. 10°, after crystallisation from acetone at −40°, b. p. 202°/4 mm., n_D^{20} 1·5430 (Found : C, 89·2; H, 10·9. $C_{22}H_{38}$ requires C, 89·2; H, 10·8%).

1 : 2 : 3-*Tri*-n-*butylnaphthalene*.—6-n-*Butyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*. *n*-Propyl 5 : 6 : 7 : 8-tetrahydro-2-naphthyl ketone was prepared in 65% yield by Barbot's method (*Bull. Soc. chim.*, 1930, **47**, 1314), but with nitrobenzene as solvent. It was obtained as a colourless oil, b. p. 177—178°/15 mm., n_D^{20} 1·5472, n_D^{25} 1·5459, m. p. +1°. Barbot gives n_D^{23} 1·5460. The 2 : 4-*dinitrophenylhydrazone* crystallised from ethyl acetate in dark red plates, m. p. 195—196° (Found : C, 62·5; H, 5·8. $C_{22}H_{28}O_4N_4$ requires C, 62·8; H, 5·8%). Huang-Minlon reduction of the ketone gave the hydrocarbon as a colourless liquid, b. p. 141°/15 mm., n_D^{20} 1·5228, in 80% yield (Found : C, 89·2; H, 10·8. Calc. for $C_{14}H_{20}$: C, 89·4; H, 10·6%). After the completion of this work, Hart and Robinson (*J. Amer. Chem. Soc.*, 1948, **70**, 3731) reported n_D^{20} 1·5234 for this hydrocarbon.

3-n-*Butyl*-5 : 6 : 7 : 8-*tetrahydro*-2-*naphthyl* n-*propyl ketone*. Friedel–Crafts conditions were again shown not to isomerise the side chain. Acylation by the normal procedure gave this *ketone* in 66% yield as a colourless oil, b. p. 153—154°/1 mm., n_D^{20} 1·5302 (Found : C, 83·7; H, 10·3. $C_{16}H_{24}O$ requires C, 83·7; H, 10·1%). The structure was proved by degradation to tetramethyl pyromellitate, by the method described for the corresponding hexanoylhexyltetralin. The red 2 : 4-dinitrophenylhydrazone, deposited from methanol on long storage at 0°, could not be purified for analysis.

6 : 7-Di-*n*-butyl-1 : 2 : 3 : 4-tetrahydronaphthalene was obtained as a colourless oil, b. p. 160—161°/1 mm., n_D^{20} 1·5174, in 70% yield (Found : C, 88·5; H, 11·5. Calc. for $C_{18}H_{28}$: C, 88·6; H, 11·5%) by the copper chromite reduction of the ketone. Hart and Robinson (*loc. cit.*) record n_D^{20} 1·5172.

2 : 3-*Di*-n-*butyl*-5 : 6 : 7 : 8-*tetrahydro*-1-*naphthyl* n-*propyl ketone*. The dibutyltetralin was acylated in 51% yield by the normal method, carbon disulphide being used as solvent. The *ketone* was obtained as a colourless oil, b. p. 190°/4 mm., n_D^{20} 1·5189 (Found : C, 83·9; H, 10·8. $C_{23}H_{34}O$ requires C, 84·1; H, 10·8%); no derivatives could be obtained.

5 : 6 : 7-*Tri*-n-*butyl*-1 : 2 : 3 : 4-*tetrahydronaphthalene*. Catalytic reduction with copper chromite, at, initially, 110 atm., followed by heating at 200° for 6 hours, gave incompletely reduced material. Repeated

hydrogenation at 240° eventually gave the *hydrocarbon* as a colourless oil, b. p. 171—172°/2 mm., n_D^{20} 1·5160, in 57% yield (Found: C, 88·2; H, 12·0. $C_{22}H_{44}$ requires C, 88·0; H, 12·0%). Use of a higher temperature and pressure (140 atm. initially, and then at 300°) gave 1 : 2 : 3-*tri*-n-*butyldecalin*, b. p. 162—164°/2 mm., n_D^{20} 1·4860 (Found: C, 86·3; H, 13·7. $C_{22}H_{42}$ requires C, 86·3; H, 13·7%). 1 : 2 : 3-*Tri*-n-*butylnaphthalene* was obtained in 70% yield by the catalytic dehydrogenation of the tributyltetralin under the conditions described for 2 : 3-di-n-hexylnaphthalene. The colourless oil, b. p. 199—200°/3 mm., n_D^{20} 1·5437, could not be obtained crystalline (Found: C, 89·1; H, 11·1. $C_{22}H_{38}$ requires C, 89·2; H, 10·8%).

The authors thank Professor Sir Robert Robinson, O.M., F.R.S., for his interest in this work, Dr. J. C. Smith for helpful discussions, and Dr. and Mrs. Richards (the Physical Chemistry Laboratory, Oxford) for determining the infra-red values. They are grateful to the Anglo-Iranian Oil Company Ltd. for financial support, and one of them (B. B.) to New College, Oxford, for a Senior Govett Scholarship, during the tenure of which the investigations, recorded in this and the preceding paper, were carried out.

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235. *Selective Oxidations with Red Lead.*

By L. VARGHA and M. REMÉNYI.

Red lead, in presence of acetic acid, can be used in many cases for the selective oxidation of glycols, α-hydroxy-acids, and certain amino-compounds in place of lead tetra-acetate or periodic acid. The procedure is demonstrated by several examples.

RED LEAD (Pb_3O_4) has been already employed in isolated cases for oxidation, *e.g.*, for introduction of acetoxy-groups into alicyclic and semialicyclic hydrocarbons (Fieser and Cason, *J. Amer. Chem. Soc.*, 1940, **62**, 432); however, oxidation of α-glycols and related compounds with this directly applicable, comparatively inexpensive oxidant appears not to have been systematically investigated. Oxidation with red lead is essentially oxidation with lead tetra-acetate under modified conditions (Vargha, *Nature*, 1948, **162**, 927) and in most of the cases the results are the same with both methods. In the present paper we report the behaviour of polyhydric alcohols, hexoses, hexosides, and some other substances in the presence of red lead in 25% acetic acid.

In dilute acetic acid the reduction and hydrolysis of transiently-formed lead tetra-acetate are competing with each other. Diethylidene sorbitol, pinacol, and phenyl-D-glucosotriazole, although consuming the oxidant in but 8—9 hours at room temperature, appeared to suppress hydrolysis completely, while with ethylene glycol, α-methylglucoside, or alanine considerable hydrolysis within a few minutes was observed. Oxidation of polyhydric alcohols and of α-hydroxy-acids proceeds as with lead tetra-acetate in glacial acetic acid; differences are observed only with free hexoses, D-glucose and D-galactose, which react with red lead under influence of the water present not as ring but as open-chain compounds, *i.e.*, as in periodic acid oxidations. Ethylenediamine and alanine remain unchanged under the conditions employed, the oxidant suffering quantitative hydrolysis, but fission of (−)-ephedrine to benzaldehyde and acetaldehyde occurred quantitatively.

Red lead oxidation is particularly successful in the simple preparation of ethyl glyoxylate from ethyl tartrate (yield, 54%), as compared with the similar oxidation with lead tetra-acetate; in the latter case the semiacetal of ethyl glyoxylate is obtained in a yield not exceeding 40—45% and the process of isolation is rather lengthy (Criegee, Kraft, and Rank, *Annalen*, 1933, **507**, 159).

Satisfactory yields have been obtained also in the preparation of 4-formyl-2-phenyltriazole from phenyl-D-glucosotriazole (Hann and Hudson, *J. Amer. Chem. Soc.*, 1944, **66**, 735, obtained this product by periodic acid oxidation) and of L-xylose from 1 : 3-2 : 4-diethylidene sorbitol (cf. Appel, *J.*, 1935, 425; Hockett and Schäffer, *J. Amer. Chem. Soc.*, 1947, **69**, 849); in the latter case the oxidation product is converted by subsequent hydrolysis into the free sugar. These examples show that even substances practically insoluble in water or sensitive towards acids can be oxidized in dilute acetic acid solution with red lead.

EXPERIMENTAL.

Experiments were carried out with technical red lead (active oxygen content being assayed by titration with N-potassium permanganate) at room temperature in 25% acetic acid (purified by distillation from powdered potassium permanganate), 1 mole of Pb_3O_4 per 8·8 moles of acetic acid being employed. Mechanically-shaken, open vessels were used. The course of the reaction was followed by means of the decoloration of the mixture and by analysis of the end products.

For determination of the volatile end-products formaldehyde, acetaldehyde, and formic acid, lead was precipitated from the mixture by sulphuric acid and the filtrate was subsequently distilled. The distillate was then titrated iodometrically to determine the aldehyde content, while titration with permanganate gave the content of aldehyde plus formic acid. Carbon dioxide was determined volumetrically. Lead dioxide was separated from the mixture by centrifugation and washed with 5% acetic acid, dried, and weighed. The rate of oxidation depends on the nature of the substance to be oxidized and on the rate of conversion of the red lead into lead tetra-acetate, *i.e.*, on the temperature and on the concentration and quantity of the acetic acid solution. The rate of oxidation increases rapidly with the initial acetic acid concentration up to 25%, but thereafter does not change significantly. Red lead itself, in absence of acetic acid, does not bring about oxidation, whereas lead dioxide in dilute acetic acid shows an unspecific oxidative effect, the rate of which, however, may be neglected in comparison with that of the tetra-acetate.

Ethyl Glyoxylate.—To a solution of ethyl tartrate (20·6 g.; 0·1 mol.) in 25% acetic acid (200 c.c.) red lead (68·6 g., 0·1 mol.) was added in small portions during *ca.* 1 hour at 15—20°, with mechanical stirring. Stirring was continued until complete decoloration (8 hours) had occurred. The clear solution was then continuously extracted with ether for 7 hours, the ethereal solution being subsequently dried and evaporated. The remaining oil gave ethyl glyoxylate, b. p. 58—62°/14 mm. (11 g., 54%).

4-*Formyl*-2-*phenyltriazole.*—A suspension of phenyl-D-glucosotriazole (1·3 g., 0·005 mol.) in 25% acetic acid (40 c.c.) was stirred at 15—20° for 8 hours, red lead (13·72 g., 0·02 mol.) being gradually added during the first hour. The resulting mixture was filtered, and the solid extracted with boiling alcohol (15 c.c.). The aldehyde crystallized from the alcoholic extract after addition of 30 c.c. of water and had m. p. 68° (0·72 g., 83%).

L-*Xylose.*—To a solution of 1 : 3-2 : 4-diethylidene sorbitol (5·85 g., 0·025 mol.) in 25% acetic acid (50 c.c.) red lead (17·5 g., 0·025 mol.) was added within 30 minutes, at 15—20° with mechanical stirring. Stirring was continued until the red lead disappeared (10 hours). Then the lead was precipitated with 50% sulphuric acid at 0° and more sulphuric acid was added until the solution became approx. 0·2N. The mixture was warmed in an open flask on the water-bath until acetaldehyde had evaporated (about 5 hours) and was then exactly neutralized with barium hydroxide. The solid was removed and washed on the centrifuge, and the solution evaporated at 14 mm. The residue was freed from water by being distilled with alcohol and then crystallized from alcohol, yielding L-xylose (2 g., 50%), m. p. 146—147°.

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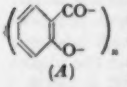
[*Received, April 26th,* 1950.]

236. *The Stereochemistry of the Salicylides and Some Related Compounds.*

By P. G. EDGERLEY and L. E. SUTTON.

Following the discovery that "α- and β-disalicylides" are not stereoisomers but are the only known forms of di- and tri-salicylides respectively (Baker, Ollis, and Zealley, *Nature*, 1949, **164**, 1049; Edgerley and Sutton, *ibid.*, p. 1050; Baker, Ollis, and Zealley, *J.*, 1951, 201), a systematic study of the electric dipole moments of these compounds, the tetrasalicylide, and of the corresponding cresotides has been made. From the results it is possible to give a consistent account of the stereochemistry of these systems. It has also been shown that there is likely to be steric hindrance between certain atoms in phenyl acetate and some related esters.

CERTAIN anhydro-derivatives of salicylic acid are known, *viz.*, (*A*) where *n* is 2, 3, 4, or more (see R. Anschütz, *Ber.*, 1919, **52**, 1880, and later works by L. Anschütz *et al.*; and, especially, Baker, Ollis, and Zealley, *Nature*, 1949, **164**, 1049; *idem* with Gilbert, *Chem. and Ind.*, 1950, 333; *J.*, 1951, 201, 208). Such compounds raise interesting stereochemical problems since, in theory, it is possible to obtain several different stereoisomeric modifications of each polymer. At the request of Professor W. Baker, we undertook the investigation of what were then thought to be the two stereoisomers of disalicylide, by measuring their dipole moments in benzene solution.

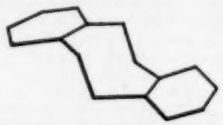


(*A*)

The *trans*-form Fig. 1*a*, should have a dipole moment of approximately zero (one might expect a small apparent moment due to atom polarisation) and the *cis*-form Fig. 1*b*, ought to have one of about 6·0—6·2 D. (see "Discussion" below). In actuality, while the compound known as α-disalicylide, to which the *cis*-configuration had been tentatively ascribed, has the predicted

dipole moment (actually 6·26 D.), the other "isomer" has a moment of 2·41 D. This high value is unlikely to arise from atom polarisation. Professor Baker and his co-workers therefore

FIG. 1*a*. FIG. 1*b*.



remeasured the molecular weight of "β-disalicylide" and showed that it is not a dimer but is a trimer, so that its dipole moment is really 2·95 D. Following this discovery, a systematic study of the salicylides and the corresponding *o*-, *m*-, and *p*-cresotides has been made in the hope of finding out more about the stereochemistry of such systems.

RESULTS.

The preparative and molecular-weight determination work which is reported elsewhere (Baker *et al.*, *locc. cit*) has indicated that each polymer is ordinarily obtainable in only one form, contrary to earlier results for the dimers. The dipole moments, in benzene solution, of di-, tri-, and tetra-salicylides and of most of the corresponding derivatives from three of the cresotic acids are shown in the annexed Table. The compounds were all sparingly soluble in benzene

	Di-.	Tri-.	Tetra-.		Di-.	Tri-.	Tetra-.
Salicylide	6·26	2·95	2·07	*m*-Cresotide	6·74	3·08	—
o-Cresotide	6·34	4·28	1·25	*p*-Cresotide	6·67	3·18	—

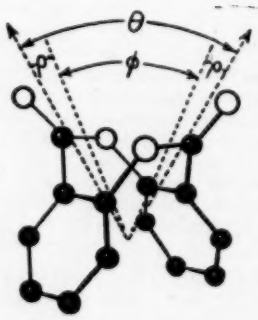
All dipole moments were measured in benzene solution at 25° and are quoted in Debye units (see Experimental section).

so it was necessary to warm the mixture to about 70° to ensure complete dissolution. There was no indication, such as the change of polarisation with time, that such treatment caused any change within the molecules.

DISCUSSION.

cis-Disalicylide is represented on Fig. 2. The geometry of ring systems of this sort is variable (see Baker, Banks, Lyon, and Mann, *J.*, 1945, 27), but, in the configuration shown, the resonance energy should be a maximum (see below) for in it the lactone groups are co-planar. The moment of the compound should then be approximately the resultant of two lactone-group moments (each of 4·1 D.; Marsden and Sutton, *J.*, 1936, 1383) at an angle θ, which can be calculated if the angles ϕ and ρ are known (see Fig. 2). The angles Ph–C–O and Ph–O–C (where O is the bridge-oxygen atom) may be assumed to lie between the limits 109·5° and 120°. Since the rest of the geometry of the molecule is determined by the benzene rings, ϕ = 64·5—70·5°. The value of ρ, which is controlled by the direction of the *cis*-ester-group moment, has been estimated by Mr. L. E. Orgel (private communication) from a molecular-orbital calculation to be about 27°. θ is therefore 82—86°, and the calculated moment is 6·2—6·0 D.

FIG. 2.



Plates I*a* and I*b* show a scale model of di-*o*-cresotide. It can be seen (Plate I*a*) that there is no interference between the methyl groups and any other atom or group of atoms in the molecule; also the two groups are in such positions (Plate I*b*) as to produce a resultant moment of zero. The small difference between the dipole moments of disalicylide and di-*o*-cresotide is not significant. It may be due to a small inductive effect or to the theoretical and practical limitations of the method. The other two isomers have their methyl groups in such positions as to increase the total moment by the same amount. It will be seen (Fig. 2) that the planes of the two benzene rings are set at an angle of 49·5—60° (for Ph–C–O and Ph–O–C = 109·5—120°) which means that the additional moment caused by the presence of the methyl groups in both di-*m*- and di-*p*-cresotides should be 0·7—0·5 D. (the dipole moment of toluene is 0·35—0·40 D). Thus the moments of the two cresotides should be 6·95—6·75 D. For both compounds, the agreement with experiment is as good as can be expected and serves further to verify the *cis*-configuration ascribed.

PLATE Ia.

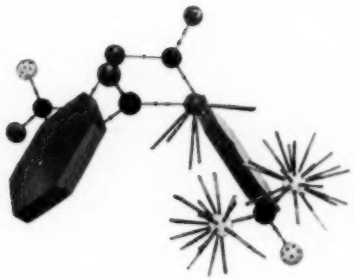


PLATE Ib.

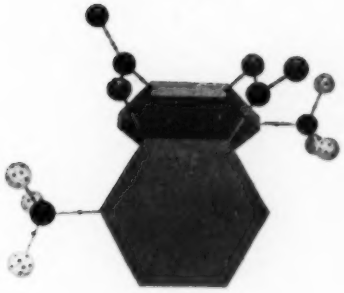
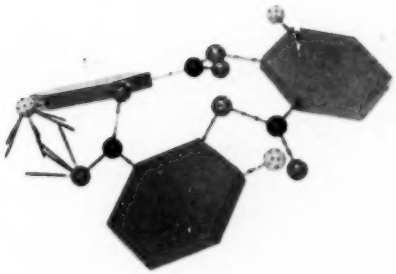


PLATE II.



[*To face p.* 1070.

For the *s*-tribenz*cyclo*dodecatriene ring system, which is similar to that of the trisalicylides, Baker, Banks, Lyon, and Mann (*loc. cit.*) showed that there is a continuous series of strainless configurations: there are two configurations of relatively high symmetry, one planar (Photograph 2A) and one trigonal (2D). From our point of view, these are especially interesting. The former contains all three ester groupings in the *trans*-configuration: * and because it is planar it is non-polar. The latter contains all three groupings in the *cis*-configuration, and it is highly polar. The other configurations may be regarded as lying between these two extremes, because they can all be shown to involve a gradual change in the relative degrees of *cis*- and *trans*-character in the ester groupings. We can distinguish an intermediate configuration with two *trans*-ester groupings and one *cis*- (2C), and another with one *trans*- and two *cis*-. From these considerations, it can be seen that the dipole moment of any configuration must lie between that for the planar, triply-*trans*-form, and that for the crown, triply-*cis*-form. The moment of the *trans*-ester grouping may be taken as that of phenyl benzoate—1·9 (Warren, *J.*, 1937, 1858)—and that of the *cis*-form as that of γ-butyrolactone—4·1 (Marsden and Sutton, *loc. cit.*). The calculated moments of the various forms are:

	Moment, D.		Moment, D.
3 *trans*-, 0 *cis*-linkages	0·0	1 *trans*-, 2 *cis*-linkages	6·5
2 *trans*-, 1 *cis*- „	4·5	0 *trans*-, 3 *cis*- „	10·0

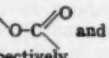
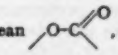
From the observed moment (2·95 D.), we may conclude that the actual configuration approaches the planar, non-polar one.

Considering now the effects of steric hindrance which hitherto have been completely ignored, we see (Plate II) that, because of steric hindrance between the carbonyl oxygen atoms and the hydrogen atoms *ortho* to the ring-oxygen atoms, it would be impossible for a planar configuration to be assumed. There is another " planar " configuration of trisalicylide with the three carbonyl groups directed towards the centre: this is also stereochemically impossible, even in a somewhat distorted form. The actual configuration can, therefore, be explained by supposing that each ester group tends to take up the *trans*-configuration, so far as steric hindrance allows; it could be such that the planes of the benzene rings would intersect at the apex of a trigonal pyramid, giving a propeller-like structure. Plate II shows the twisting effect on one of the ester linkages of the overlapping of the van der Waals radii of the hydrogen atom and of the carbonyl oxygen atom † (see below): it also shows the arrangement of the whole molecule.

It is clear that tri-n_g-cresotide and tri-*p*-cresotide adopt the same configuration, for their dipole moments differ only by small amounts from that of trisalicylide. This is in agreement with the above explanation: for the additional methyl groups would not cause further steric hindrance. The *o*-isomer is interesting, in that the hydrogen atom, which in trisalicylide interferes with the carbonyl oxygen atom, is now replaced by the larger methyl group; this gives rise to a stronger repulsion of the carbonyl oxygen atom, which forces the system still further out of a plane and so causes a higher moment (4·28 instead of 2·95).

Rough calculations show that if it is assumed that the distance between the centres of the sterically interfering hydrogen and carbonyl oxygen atoms is the sum of Pauling's van der Waals radii, then the C=O bond is deflected out of the plane of the benzene ring attached to the ring oxygen atom by about 50°, which means that trisalicylide should have a dipole moment of 3·7 D. If the distances are taken as 0·2—0·3 A. less than these sums, the calculated moment agrees with that observed. A similar calculation for tri-*o*-cresotide shows that there is an out-of-plane deflection of the carbonyl bond of about 90°, which corresponds to a dipole moment of 4·8 D. If an overlap of 0·5 A. is permissible, then the moment approximates to the value observed. Rough though these calculations are, they serve further to confirm the postulate of steric hindrance in the trimers. The overlap or " contraction " of the van der Waals radii is to be expected. It has been observed before that the use of van der Waals radii in investigating steric hindrance tends to exaggerate the actual interference. Stanley and Adams (*J. Amer. Chem. Soc.*, 1930, **52**, 1200) find that a difference of 0·39 A. or more between the actual and the calculated van der Waals distances is normally necessary and sufficient for optical isomers to be obtainable in the diphenyls with *o*-substituents.

These conclusions are supported by the infra-red spectra of the substances (Short, to be

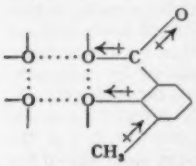
* *trans* is used to mean  and *cis* to mean  , these being the structures with the *lower* and the *higher* moment respectively.

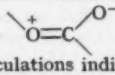
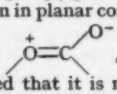
† Values for the van der Waals radii are taken from L. Pauling, " The Nature of the Chemical Bond," Cornell, 1940.

published). In the trimers and tetramers the carbonyl-bond frequency is close to where it is normally observed in esters with the exception of tri-*o*-cresotide, where it is somewhat higher. This is in good agreement with the above explanation of the high dipole moment of this compound. The still higher carbonyl-bond frequencies in the dimers is likely to be a result of the presence of *cis*-linkages as opposed to *trans*- or distorted *trans*-linkages.

It seems that tetrasalicylide ($\mu = 2{\cdot}07$) does not take up a propeller-like structure analogous to that of trisalicylide for the moment of tetra-*o*-cresotide ($\mu = 1{\cdot}25$) is less and not greater than that of the parent salicylide. From the carbonyl-bond frequencies of the two compounds, it appears that the configuration of the ester linkages is likely to be of the *trans*-type (see above); furthermore as the frequencies are about the same it is unlikely that any steric hindrance in the former is aggravated in the latter. Baker, Ollis, and Zealley (*J.*, 1951, 201) have suggested a configuration for the tetrasalicylide in which planar O·C_6H_4·CO· units are arranged alternately up and down round a central ring of four oxygen atoms. This would normally have an axis of alternating symmetry and be non-planar; but from a model it seems likely that it could lose symmetry by movements of the units parallel to the axis of rotation, and that this could result in considerable change in configuration with relatively little change in the ether-oxygen valency angles. They therefore suggested further that the appreciable dipole moment of the tetrasalicylide is apparent rather than real, and arises from an abnormally large atom polarisation (cf. Coop and Sutton, *J.*, 1938, 1269).

Some support is given to this hypothesis by the moment of the tetra-*o*-cresotide being *less* than that of the tetrasalicylide. The vibrating moments effective in giving rise to atom polarisation in the latter would be those of the four O·C_6H_4·CO units perpendicular to the respective O . . . . . O lines, *i.e.*, the moments of two C–O bonds less μ (C=O) sin 30°; and our estimate of this is between 0·68 and 0·40. The effective component of the nuclear *o*-methyl group is 0·4 sin 30° = 0·2 and it would *reduce* the vibrating component. The ratio of the apparent moments for the salicylide and cresotide should therefore be between 0·68 : 0·48 and 0·40 : 0·20, *i.e.*, between 1·3 and 2·0. The actual value is 1·65. It must be emphasised, however, that the vibrating components are individually small, and that therefore, although there are four of them, for this hypothesis to be correct the force constant controlling the vibration must be very small indeed, *i.e.*, there must be very little change in the valency angles as the distortion occurs.



It remains to attempt to explain why each polymer can ordinarily be obtained in only one form, so far as is known, and why it takes up the particular form that it does. In a previous paper by Marsden and Sutton (*loc. cit.*), it was shown that the ester linkage always takes up the *trans*-configuration when there is a free choice. In lactones, however, owing to the restriction imposed by the ring, the *cis*-form is assumed; and, since this appears true even in the ε-lactone where the restriction is less complete, it seems that the ester grouping takes up either the *trans*- or the *cis*-configuration but no intermediate one. The fixation in planar configurations was explained by resonance involving the structure  or  , which has double-bond character in the O–C link. Rough calculations indicated that it is necessary to surmount an energy barrier of 5·5—7·5 k.cals./mole in order to pass from one configuration to the other. Thus it can be readily seen why it is not easy to pass from one polysalicylide configuration to another; furthermore, in the dimer the molecule would have to pass through a highly strained intermediate state for the change to happen. The preference for the *trans*-configuration when apparently there is free choice was not explained: but, for the present, we may take it as an empiricism that this preference exists.

In the dimer the ester groupings cannot be planar if the molecule as a whole is *trans*, so much of the resonance energy is lost because the ester groups are twisted out of planarity. In this case, therefore, the *cis*-configuration of the molecule is the more stable for in it, though the ester groups are *cis*, they are planar. In the trimers and tetramers, the configurations with triply- or quadruply-*cis*-ester groups could have these planar, though, as we have seen, because of steric hindrance, co-planarity is not possible if the ester groups are all *trans*. It must, therefore, be supposed that the "*trans* preference" postulated above overweighs the loss of resonance energy when the groups are imperfectly *trans* to this degree. While it is still not possible to give a convincing explanation of this preference in the case of the aliphatic esters, there is a factor in the aromatic compounds discussed in this paper which could cause it or augment it.

In the salicylides and cresotides, there could be conjugation of each ester group with the two phenyl groups attached to it, if the whole system were co-planar. For the dimers, this is impossible for either the *cis*- or the *trans*-configuration : so it need not be taken into account. For the trimers and tetramers, it is not, in fact, completely possible in any configuration : but whereas in the triply-*cis*-configuration, *neither* ring can resonate with an ester grouping, in the distorted triply-*trans*-configuration, one ring can do it with each ester grouping. Therefore, there may be resonance in the latter (involving benzene rings) which is absent in the former and this may compensate for the loss of stabilisation in the latter caused by the ester groups themselves being imperfectly planar (see above). The balance of energy, when steric repulsion is taken into account, may well favour a distorted triply-*trans*-configuration.

It is relevant to remark here that there can only be limited resonance between the ester grouping and the benzene ring in phenyl acetate ($\mu = 1{\cdot}6$), because there is interference between the carbonyl-oxygen and the hydrogen atom in the *ortho*-position, which inhibits the co-planar configuration, just as in trisalicylide. The moment, therefore, far from being anomalous, as was previously thought (Donle, *Z. physikal. Chem.*, 1931, *B*, **14**, 326; Marsden and Sutton, *loc. cit.*) because it is not greater than that of methyl acetate ($\mu = 1{\cdot}7$), should be no different apart from a small induced moment. Correspondingly the moments of phenyl benzoate and methyl benzoate should be equal as, in fact, they are.

In the tetramer there is, besides resonance (*a*) in the ester group and (*b*) with benzene rings, and steric repulsion, a fourth factor, *viz.*, bond strain energy. It is hardly possible to predict what the result of their interplay should be.

Experimental.

All the compounds were supplied by Professor W. Baker, Dr. W. D. Ollis, and their co-workers of the University of Bristol. Their methods of preparation and purification have been described (*Nature*, 1949, **164**, 1049; *Chem. and Ind.*, 1950, 333; *J.*, 1951, 201, 208).

Solvent purification and polarisation measurements were carried out in the manner described by Everard and Sutton (*J.*, 1949, 2312). The refractive indices of the solutions were determined on a Pulfrich refractometer. The calculations of the polarisations were performed by the methods advocated by Everard, Hill, and Sutton (*Trans. Faraday Soc.*, 1950, **46**, 417). The symbol convention is the same as in the last-mentioned paper, *viz.*, ω, ε, v, and n refer respectively to the weight fraction of solute and the dielectric constant, the specific volume, and the refractive index of the solution, and α, β, and γ are defined by the least square plots of the equations $\varepsilon = \varepsilon_1 + \alpha\omega$, $v = v_1 + \beta\omega$, and $n = n_1 + \gamma\omega$.

ω.	ε.	v.	Δn.	ω.	ε.	v.	Δn.
Disalicylide (*formerly α-disalicylide*) (I).				*Trisalicylide* (*formerly β-disalicylide*) (II).			
0·00066	2·2850	1·14464	—	0·00150$_5$	2·2759	1·14448	—
0·00149	2·2993	1·14435	—	0·00292	2·2796	1·14393	—
0·00290	2·3241	1·14385 *	—	0·00333	—	—	0·00033
0·00360	—	—	0·00027	0·00353	2·2818	1·14360	—
0·00395$_5$	2·3442	1·14355 *	—	0·00463	2·2849	1·14306	—
Tetrasalicylide (III).				*Di-o-cresotide* (IV).			
0·00089	2·2738	1·14383	—	0·00	—	1·14453	—
0·00158	2·2746	1·14362	—	0·00097	2·2892	1·14425	—
0·00344	2·2771	1·14293	0·00043	0·00163	2·2993	1·14386	—
				0·00203	2·3062	1·14368	—
				0·00390	2·3372	1·14314	0·00029
Tri-o-cresotide (V).				*Tetra-o-cresotide* (VI).			
0·00	—	1·14583	—	0·00	—	1·14438	—
0·00104	2·2769	1·14537	—	0·00145	2·2740	1·14380	—
0·00338	2·2888	1·14441	0·00023	0·00272$_5$	2·2749	1·14341	—
0·00584	2·3015	1·14338	0·00040	0·00387	2·2752	1·14296	0·00021
Di-m-*cresotide* (VII).				*Tri*-m-*cresotide* (VIII).			
0·00	—	1·14453	—	0·00	—	1·14483	—
0·00166	2·3049	1·14395	—	0·00119	2·2759	1·14422	—
0·00248	2·3190	1·14359	—	0·00227	2·2791	1·14374	—
0·00390	2·3453	1·14308	0·00026	0·00399	2·2840	1·14302	0·00038
Di-p-*cresotide* (IX).				*Tri*-p-*cresotide* (X).			
0·00129	2·2961	1·14428	—	0·00	—	1·14478	—
0·00239	2·3164	1·14389	—	0·00117	2·2760	1·14419	—
0·00383	2·3427	1·14335	0·00028	0·00269	2·2803	1·14370	—
				0·00407	2·2845	1·14314	0·00033

* Values obtained by extrapolation.

Dipole moments of the salicylides and related compounds.

	α.	ϵ_1.	$-\beta$.	v_1.	γ.	$_1P_2$.	$_2P_2$.	μ.
(I) ...	17·914	2·2728	0·34	1·14495	0·074	866·5	66·3	6·26 ± 0·02
(II) ...	2·909	2·2714	0·45	1·14520	0·100	271·4	93·6	2·95 ± 0·03
(III) ...	1·239	2·2727	0·35	1·14415	0·102	225·7	139·9	2·07 ± 0·05
(IV) ...	16·458	2·2729	0·36	1·14450	0·073	893·3	72·9	6·34 ± 0·02
(V) ...	5·124	2·2715	0·41	1·14579	0·068	475·8	101·9	4·28 ± 0·04
(VI) ...	0·499	2·2733	0·35	1·14432	0·061	172·9	140·1	1·25 ± 0·10
(VII) ...	18·572	2·2727	0·38	1·14455	0·071	998·8	71·2	6·74 ± 0·02
(VIII) ...	2·834	2·2727	0·45	1·14479	0·093	297·7	103·7	3·08 ± 0·03
(IX) ...	18·306	2·2727	0·38	1·14480	0·074	984·9	71·4	6·67 ± 0·02
(X) ...	2·897	2·2726	0·39	1·14473	0·080	309·8	107·4	3·18 ± 0·04

The authors thank the Ministry of Education for a grant to one of them (P. G. E.) and Imperial Chemical Industries Limited for a grant towards the cost of the research.

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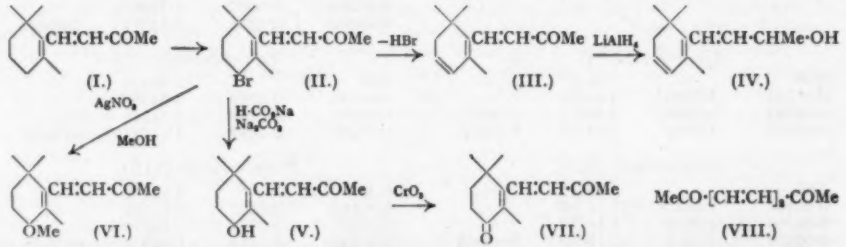
237. *Studies in the Polyene Series. Part XXXVII. Preparation of 3-Dehydro-β-ionone and Some 3-Substituted β-Ionones.*

By H. B. HENBEST.

The reaction between β-ionone and *N*-bromosuccinimide yields a 3-bromo-compound, converted by dehydrobromination into 3-dehydro-β-ionone and by hydrolysis and methanolysis into 3-hydroxy- and 3-methoxy-β-ionone, respectively. Oxidation of the 3-hydroxy-compound gives 3-keto-β-ionone, identical with that prepared by Prelog and Meier (*Helv. Chim. Acta*, 1950, **33**, 1276) by a biological oxidation of β-ionone.

THE preparation of 3-dehydro-β-ionone (III), by bromination of β-ionone (I) with *N*-bromosuccinimide followed by dehydrobromination of the resulting bromo-compound with diethylaniline, was reported in a preliminary communication (Henbest, *Nature*, 1948, **161**, 481). Since that time, efforts have been directed towards improving the yield and purity of this ketone in view of the possible use of the reaction sequence for the synthesis of vitamin A_2 (cf. Farrar, Hamlet, Henbest, and Jones, *Chem. and Ind.*, 1951, 49).

However, in the meantime, two publications dealing with the bromination of β-ionone with *N*-bromosuccinimide have appeared. Karrer and Ochsner (*Helv. Chim. Acta*, 1948, **31**, 2093) describe the treatment of β-ionone with two molecular proportions of *N*-bromosuccinimide (one molecular proportion of the bromo-imide giving some unchanged β-ionone), followed by dehydrobromination with boiling diethylaniline. The products isolated were 1 : 2-dihydro-1 : 1-dimethylnaphthalene and 4-2′ : 3′ : 6′-trimethylphenylbutan-2-one. Büchi, Seitz, and



Jeger (*ibid.*, 1949, **32**, 39) performed the reaction with one molecular proportion of *N*-bromosuccinimide, and the dehydrobromination with silver oxide or dimethylaniline at 90°. The 3-dehydro-β-ionone (III) so formed was isolated as its crystalline phenylsemicarbazone, from which it was regenerated by steam-distillation with phthalic anhydride. Confirmation of structure (III) for the ketone was obtained by ozonolysis, whereupon αα-dimethylsuccinic acid was isolated in 30% yield.

The method of preparing 3-dehydro-β-ionone, reported in the preliminary communication has now been considerably improved, both in yield and purity of product. The published physical constants of 3-dehydro-β-ionone and certain of its derivatives are listed in Table I, together with the constants for the best sample of the ketone now obtained by the improved procedure, and the corresponding values for pure β-ionone and its derivatives. Comparison of the second and third columns of the Table shows that, as the method of preparation has been improved, the refractive index and the value of the extinction coefficient in the 3400-A. region have been increased.

This considerable improvement in the purity of dehydro-β-ionone has been largely brought about by ensuring that no β-ionone escapes reaction with *N*-bromosuccinimide. It has been found necessary to employ more than one molecular proportion of the bromo-imide, a 20% excess giving the best yield of final product. The excess of *N*-bromosuccinimide is probably mostly consumed by a side reaction whereby the methyl group adjacent to the carbonyl group is brominated.

TABLE I.

	3-Dehydro-β-ionone.			β-Ionone.
	Büchi *et al.*	Henbest (*loc. cit.*).	This paper.	This paper.
B. p.	71°/0·1 mm.	75°/1 mm.	75°/1 mm.	75°/1 mm.
n	n_D^{21} 1·5389	n_D^{23} 1·5497	n_D^{23} 1·5595	n_D^{1} 1·5227
Light absorption :				
Maximum; λ, A. (ε)	2230 (5,600)	2210 (7,200)	2240 (5,300)	2150 (7,400)
Minimum; λ, A. (ε)	—	2610 (2,700)	2640 (2,000)	2500 (1,900)
Maximum; λ, A. (ε)	3430 (4,500)	3380 (9,100)	3450 (12,200)	2960 (10,400)
M. p. :				
Semicarbazone	144°	144—146°	137—142°	147—149°
2 : 4-Dinitrophenylhydrazone	—	150—151	150—151	129—130
Phenylsemicarbazone	148	—	147—150	—

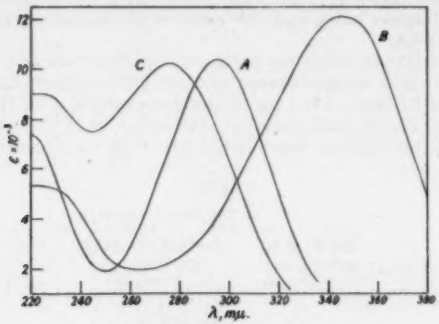
The dehydrobromination stage was effected smoothly and quickly with diethylaniline at 100°, and the crude dehydro-β-ionone so obtained was purified through its semicarbazone. Separate tests had shown that the mixed semicarbazones of β-ionone and 3-dehydro-β-ionone cannot be separated by crystallisation, mixtures of the two crystallising to give products with melting points intermediate between those of the pure derivatives. Thus it was important to have no unreacted β-ionone in the crude dehydro-ketone. On the other hand, the dehydro-ketone 2 : 4-dinitrophenylhydrazone can be purified by crystallisation; it has a higher melting point than that of the corresponding β-ionone derivative. Regeneration of the ketone from its crystalline semicarbazone was best effected by dilute acid at room temperature (Heilbron, Johnson, Jones, and Spinks, *J.*, 1942, 727). As already noted by Young and Linden (*J. Amer. Chem. Soc.*, 1947, **69**, 2072) this method is preferable to those involving steam-distillation with phthalic or oxalic acid for the hydrolysis of polyene semicarbazones.

Crude 3-bromo-β-ionone, as obtained from the bromination of β-ionone, has been converted into a number of other 3-substituted β-ionones as outlined in the scheme above. The bromo-compound reacted readily with sodium formate at room temperature to give a 3-formoxy-compound (not isolated) which was converted by mild alkaline hydrolysis into 3-hydroxy-β-ionone (V). 3-Methoxy-β-ionone (VI) was obtained when the 3-bromo-compound was added to a solution of silver nitrate in methanol [cf. the preparation of 7-methoxy-steroids (Henbest and Jones, *J.*, 1948, 1798)].

3-Hydroxy-β-ionone was easily oxidised in acetone solution with chromic acid (cf. Bowden, Heilbron, Jones, and Weedon, *J.*, 1946, 39) to give the crystalline 3-keto-β-ionone (VII). A compound, to which a 3-keto-β-ionone structure was assigned, has recently been isolated from the urine of rabbits which had been fed on a diet containing β-ionone (Prelog and Meier, *loc. cit.*). The physical constants of the diketone obtained by this biological oxidation of β-ionone agreed well with those of our compound, and a mixed-m. p. determination confirmed their identity. The Swiss workers also obtained a hydroxy-ketone from the same experiment, the analysis and ultra-violet light absorption properties of which indicated the structure either of a 3-keto-β-ionol or a 3-hydroxy-β-ionone, the former structure being preferred on the basis of infra-red spectroscopic data. A comparison of the phenylsemicarbazone of Prelog and Meier's hydroxy-ketone (m. p. 174—175°) with the phenylsemicarbazone of 3-hydroxy-β-ionone (m. p. 153—154°) prepared in this work showed that the higher-melting compound was indeed a

derivative of 3-keto-β-ionol, the non-identity of the two compounds being further confirmed by a marked depression in a mixed-m. p. determination. These mixed-m. p. determinations were kindly carried out by Professor Prelog.

3-Keto-β-ionone is of further interest in that it may be possible to insert another keto-group in the 4-position, thus yielding a compound with a ring structure identical with the



A : *β-Ionone.*
B : *3-Dehydro-β-ionone.*
C : *3-Keto-β-ionone.*

terminal ring systems in the carotenoid, astacene (Karrer *et al.*, *Helv. Chim. Acta*, 1936, **19**, 479, and earlier papers).

The light-absorption properties of the compounds prepared in this work are listed in Table II. It is evident that these substituted β-ionones exhibit " anomalous " light-absorption properties similar in character to that shown by β-ionone itself. For instance, the main absorption band of dehydro-β-ionone is located in a position similar to where a triply unsaturated ketone of this type would be expected to display maximal absorption, but the intensity of absorption is very much reduced. Moreover, dehydro-β-ionone, like β-ionone (see figure),

TABLE II.

	Compound.			Semicarbazone.			2 : 4-Dinitrophenylhydrazone.		
	Max.	Min.	ε.	Max.	Min.	ε.	Max.	Min.	ε.
β-Ionone	2150		3,400	2150		8,100	2150		17,100
								2820	11,300
		2500	1,900		2350	2,900	2900		11,600
								3230	5,600
	2960		10,400	2810		22,200	3860		29,200
3-Dehydro-β-ionone					2280	5,900			
	2240		5,300	2590		12,200	2150		15,600
								2330	14,400
		2640	2,000		2720	8,500	2500		14,900
								2870	8,000
	3450		12,200	3250		18,700	3980		30,800
3-Hydroxy-β-ionone							2190		16,800
								2820	11,500
		2500	4,200		2350	6,900	2880		11,600
								3180	5,100
	2870		8,000	2775		22,800	3815		28,600
3-Methoxy-β-ionone	2180		9,800	2170		8,200	2170		18,000
								2830	11,600
		2500	4,000		2340	6,700	2880		11,700
								3180	5,100
	2840		8,000	2760		23,800	3820		29,200
3-Dehydro-β-ionol		2350	2,100						
	2850		8,400						
3-Keto-β-ionone	2200		8,900						
		2450	7,500						
	2770		10,200						
2 : 7-Diketo-octa-3 : 5-diene *	2760		33,200						

Wave-lengths are in A.

* Karrer, Eugster, and Perl, *Helv. Chim. Acta*, 1949, **32**, 1013.

shows a subsidiary absorption band in the 2200-A. region, which is not found in acyclic unsaturated ketones. The deviation from "normal" behaviour of the light-absorption properties of these substituted β-ionones and their derivatives can be explained, as for β-ionone and its derivatives, by steric inhibition of resonance (Braude, Jones, Koch, Richardson, Sondheimer, and Toogood, *J.*, 1949, 1890). According to these authors, the unsaturated side-chain is displaced out of the plane of the ring by the neighbouring methyl groups, thus severely restricting resonance and leading to diminished absorption intensities, and also to the appearance of bands due to partial chromophores. Similarly, the position of the main absorption band of 3-keto-β-ionone is close to that of the analogous acyclic compound, 2 : 7-diketo-octa-3 : 5-diene (VIII), but the intensity is very much reduced.

Experimental.

(M. p.s were determined on a Kofler block and are corrected; the light-absorption data were determined in ethanol solution with a Beckman spectrophotometer.)

4-2′ : 6′ : 6′-*Trimethylcyclohexa*-1′ : 3′-*dienylbut*-3-*en*-2-*one* (3-*Dehydro*-β-*ionone*) (III).—A solution of β-ionone (96 g.) in carbon tetrachloride (250 c.c.) was warmed until boiling commenced, in a flask fitted with a reflux condenser. Finely powdered *N*-bromosuccinimide (110 g.) (recrystallised from water and dried) was added in eleven equal portions, each addition being made when the exothermic reaction caused by the previous portion had subsided. When the reaction resulting from the addition of the last portion had finished, the pale-brown solution suddenly became dark brown. The mixture was immediately cooled to 30°, and light petroleum (100 c.c.; b. p. 40—60°) added to complete the precipitation of succinimide. The latter (62 g.) was filtered off, the filtrate being added directly to diethylaniline (150 c.c.). Owing to the instability of the bromo-compound(s), these last operations were carried out as quickly as possible. The deep-brown solution was warmed under reduced pressure (water-pump) to remove the light petroleum and most of the carbon tetrachloride, and the residue was heated (internal temperature 96°) on a steam-bath for 45 minutes. Diethylaniline hydrobromide crystallised out either during the heating or when the mixture was seeded. Dry pyridine (50 c.c.) was added and the mixture was heated for a further 30 minutes. The product was isolated by the addition of light petroleum (b. p. 40—60°) and sufficient 5N-hydrochloric acid to extract the organic bases. The petroleum solution was processed in the usual manner and the residue distilled from a Claisen flask with a low wide, water-jacketed side arm. The golden-yellow product (55—60 g.) had b. p. 97—100°/2 mm., n_D^{23} 1·553. For purification, it was dissolved in a solution of semicarbazide acetate [from semicarbazide hydrochloride (40 g.) and potassium acetate (40 g.)] in 80% methanol. After being kept overnight, the product was recrystallised from 80% methanol and gave the pure *semicarbazone* (54—58 g.), m. p. 137—142° (Found: C, 67·7; H, 8·65. $C_{14}H_{21}ON_3$ requires C, 68·0; H, 8·55%).

The finely powdered semicarbazone (41 g.) was shaken with light petroleum (150 c.c.; b. p. 40—60°) and 3N-sulphuric acid (150 c.c.) for two days in nitrogen and shielded from light. The mixture was filtered and the recovered semicarbazone was again powdered and shaken with petroleum (100 c.c.) and 3N-sulphuric acid (100 c.c.) for three days. Unchanged semicarbazone (5·2 g.) was then recovered; concentration of the petroleum extracts followed by distillation gave 3-*dehydro*-β-*ionone* (24·5 g.) as a yellow liquid with an odour similar to but sweeter than that of β-ionone; it had b. p. 75°/mm., n_D^{19} 1·5595 (Found: C, 82·15; H, 9·75. $C_{13}H_{18}O$ requires C, 82·1; H, 9·55%).

Pyridine was added at the end of the dehydrobromination stage to quaternise (and render water soluble) unreacted bromo-compounds (probably of the α-bromo-ketone type mentioned in the theoretical section), pyridine being more reactive in this way than diethylaniline. If the pyridine treatment was omitted, the unreacted bromo-compounds present in the crude 3-dehydro-β-ionone decomposed violently with evolution of hydrogen bromide before all the ketone had distilled over. This hazard could also be avoided by isolating the ketone by steam-distillation, a more tedious process.

The 2 : 4-*dinitrophenylhydrazone* prepared at room temperature crystallised from ethanol or ethyl acetate–methanol in dark-red needles, m. p. 150—151° (Found: C, 61·3; H, 6·15. $C_{19}H_{22}O_4N_4$ requires C, 61·6; H, 6·0%).

The phenylsemicarbazone, prepared in ethanol containing a little acetic acid, crystallised from methanol in plates, m. p. 147—150° (Büchi, Seitz, and Jeger, *loc. cit.*, give m. p. 148°). Light absorption: Maxima, 2380, 2750, and 3200 A.; ε = 16,500, 15,900, and 16,400; Minima, 2520 and 3000 A.; ε = 12,500 and 15,500.

4-2′ : 6′ : 6′-*Trimethylcyclohexa*-1′ : 3′-*dienylbut*-3-*en*-2-*ol* (3-*Dehydro*-β-*ionol*) (IV).—A mixture of 3-dehydro-β-ionone (1 g.) and dry ether (10 c.c.) was cooled to −40°, and an ethereal solution of lithium aluminium hydride (0·34M.; 5 c.c.) was added dropwise with stirring during fifteen minutes, the internal temperature being maintained at −40°. After a further fifteen minutes at this temperature, the solution was allowed to warm to 10°. A few drops of ethyl acetate were added to decompose the excess of lithium aluminium hydride, and the product was isolated with ether. Distillation gave the *carbinol* (0·65 g.), b. p. 75°/0·01 mm., n_D^{17} 1·5381 (Found: C, 80·95; H, 10·3. $C_{13}H_{20}O$ requires C, 81·2; H, 10·5%).

4-3′-*Hydroxy*-2′ : 6′ : 6′-*trimethylcyclohex*-1′-*enylbut*-3-*en*-2-*one* (3-*Hydroxy*-β-*ionone*) (V).—Pure, finely powdered *N*-bromosuccinimide (20 g.) was added to a solution of β-ionone (19·2 g.) in chloroform (50 c.c.; $CaCl_2$-dried) in a flask fitted with a reflux condenser, and the mixture warmed with gentle swirling until the reaction started. As soon as the exothermic reaction had subsided, the mixture was cooled, light petroleum (50 c.c.; b. p. 40—60°) was added, and the mixture filtered directly into a solution of sodium formate (9 g.) in 90% formic acid (50 c.c.), the succinimide being washed with more light petroleum. The reaction mixture (now in two layers) was evaporated under reduced pressure (water-pump)

at 30° or below to remove the light petroleum and most of the chloroform. Dioxan (25 c.c.) was added and the still slightly heterogeneous mixture vigorously stirred at room temperature for 2 hours. The formoxy-compound was isolated with ether, and then dissolved in methanol (200 c.c.) and added to a solution of anhydrous sodium carbonate (15 g.) in water (200 c.c.), the mixture being shaken overnight. Light petroleum (30 c.c.; b. p. 40—60°) was added and the mixture shaken. The petroleum layer, containing most of the dark colour, was separated and rejected. The hydroxy-β-ionone was then isolated from the aqueous methanol layer with ether. The crude pale-brown syrup (16·0 g.) was chromatographed on a column of alumina (Peter Spence, Grade H; 40 × 3·6 cm.). Development with light petroleum (b. p. 40—60°)–benzene (2 : 1) gave a chromatogram with the following appearance : (*a*) a small dark-brown band at the top, (*b*) a large pale-brown zone in the middle, and (*c*) two brown bands and a yellow band at the bottom. The column was allowed to drain and zones (*a*) and (*c*) were removed and rejected. The alumina of zone (*b*) was eluted with ether–methanol (9 : 1) to give a fairly pure product (12·2 g.), n_D^{18} 1·5315. Regeneration from the powdered semicarbazone (0·75 g.) (see below) by shaking it with benzene (15 c.c.) and 3N-sulphuric acid (10 c.c.) for four hours at room temperature in an atmosphere of nitrogen gave the pure *ketone* (0·46 g.) as a nearly odourless, viscous liquid, b. p. 131—132°/0·02 mm., n_D^{18} 1·5358 (Found : C, 75·0; H, 9·95. $C_{13}H_{20}O_2$ requires C, 74·95; H, 9·7%).

The semicarbazone was prepared from the crude ketone and semicarbazide acetate in methanol–water (1 : 1) at room temperature for two hours, the solution being finally cooled to 0° to obtain a better yield. Recrystallisation from methanol–water (5 : 2) or nitromethane gave the *semicarbazone* as a very pale yellow, granular solid, m. p. 182—183·5° (Found : C, 62·75; H, 8·65; N, 16·0. $C_{14}H_{23}O_2N_3$ requires C, 63·45; H, 8·75; N, 15·85%). This semicarbazone crystallised very slowly from supersaturated solutions.

The *phenylsemicarbazone*, prepared in ethanol containing a little acetic acid, was crystallised from methanol and then from benzene giving fine needles. To obtain consistent values for the melting point it was necessary to dry the samples at 80°/10^{-3} mm. for 2 hours. The pure derivative had m. p. 153—154° (Found : C, 70·7; H, 7·35. $C_{20}H_{27}O_2N_3$ requires C, 70·35; H, 7·95%). Light absorption : Maxima, 2340 and 2870 A.; ε = 16,300 and 27,400 : Minima, 2120 and 2510 A.; ε = 10,900 and 10,300. On admixture with 3-keto-β-ionol phenylsemicarbazone (m. p. 174—175°) the melting point was depressed to 134—135°.

The 2 : 4-*dinitrophenylhydrazone* crystallised in dark-red needles, m. p. 137—138°, from methanol-ethyl acetate (3 : 1) (Found : C, 58·5; H, 6·65. $C_{19}H_{24}O_5N_4$ requires C, 58·75; H, 6·25%).

4-3′-*Keto*-2′ : 6′ : 6′-*trimethyl*cyclo*hex*-1-′*enyl*-*but*-3-*en*-2-*one* (3-*Keto*-β-*ionone*) (VII).—A solution of chromic acid (3·5 c.c.) [prepared by dissolving chromic acid (10 g.) in a mixture of concentrated sulphuric acid (9 c.c.) and water (40 c.c.)] was added with stirring at 0° to a solution of 3-hydroxy-β-ionone (2·08 g.) in dry (K_2CO_3) AnalaR acetone (30 c.c.) during five minutes. The oxidation was very rapid, and after a further two minutes, water was added and the organic product isolated with ether. The oily product was dissolved in methanol–water (20 c.c.; 5 : 2) and cooled to −30°, whereupon a granular solid separated. This was recrystallised from light petroleum (b. p. 40—60°) (solution at 25° cooled to −25°) and methanol–water (1 : 1) (solution at 35° cooled to −10°) and gave the diketone (0·44 g.) in lustrous plates, m. p. 51—52° (Found : C, 75·3; H, 8·75. Calc. for $C_{13}H_{18}O_2$: C, 75·7; H, 8·8%). On admixture with Prelog and Meier's diketone (m. p. 52—53°) the melting point was 52—53°.

4-3′-*Methoxy*-2′ : 6′ : 6′-*trimethyl*cyclo*hex*-1′-*enyl*-*but*-3-*en*-2-*one* (3-*Methoxy*-β-*ionone*) (VI).—β-Ionone (9·6 g.) was brominated as described for the preparation of 3-hydroxy-β-ionone, and the mixture, after being cooled to 25°, was filtered into a methanolic solution of silver nitrate, prepared by dissolving silver nitrate (12 g.) in the minimum quantity of warm water and adding this solution to methanol (400 c.c.) at 25°. There was an immediate precipitation of silver bromide, and, after being gently stirred for 5 minutes, the mixture was filtered, and the silver bromide washed with light petroleum (b. p. 40—60°). The filtrate was diluted with water, and the product isolated with light petroleum (b. p. 40—60°). After concentration, the petroleum solution was passed down a column of alumina (200 g.; Peter Spence, Grade O), the column being developed with light petroleum (b. p. 40—60°). This treatment removed any hydroxy-compounds present as well as some coloured impurities. The petroleum eluate was concentrated under reduced pressure (water-pump), and the residue dissolved in aqueous methanol containing semicarbazide acetate. This solution was then kept at −8° for several days, during which time a solid product slowly separated. The collected solid was recrystallised from ethanol, giving the crystalline *semicarbazone* (3·5 g.), m. p. 165—167° (Found : C, 64·25; N, 9·55. $C_{15}H_{25}O_2N_3$ requires C, 64·5; H, 9·0%).

Pure 3-*methoxy*-β-*ionone* (0·17 g.) was obtained by shaking the powdered semicarbazone (0·25 g.) with light petroleum (10 c.c.; b. p. 40—60°) and 2N-sulphuric acid (10 c.c.) for 4 hours. The ketone was obtained as a liquid with an odour similar to, but much fainter than, that of β-ionone; it had b.p. 95°/0·02 mm., n_D^{17} 1·5161 (Found : C, 75·6; H, 10·1. $C_{14}H_{22}O_2$ requires C, 75·65; H, 10·25%).

The 2 : 4-*dinitrophenylhydrazone*, prepared by adding the semicarbazone to a warm solution of 2 : 4-dinitrophenylhydrazine in methanolic sulphuric acid, crystallised from methanol–ethyl acetate (1 : 1) in fine, dark-red needles, m. p. 140—141° (Found : C, 59·85; H, 6·25. $C_{20}H_{28}O_5N_4$ requires C, 59·7; H, 6·5%).

The author is indebted to Professor E. R. H. Jones, F.R.S., for advice and encouragement and to Professor V. Prelog for carrying out the mixed-m. p. determinations.

THE UNIVERSITY, MANCHESTER, 13. [*Received, October 24th*, 1950.]

238. *Synthetic Long-chain Aliphatic Compounds. Part III. A Critical Examination of Two Methods of Synthesis of Olefinic Acids.*

By D. E. Ames and R. E. Bowman.

Syntheses of olefins, acyloins and alkoxy-ketones being used as intermediates, have been submitted to a careful scrutiny at each stage, whereby techniques have been developed for the preparation of unsaturated acids of a high degree of purity. The acyloin route is to be preferred for the straight-chain acids since it allows the separate preparation of *cis*- and *trans*-isomers *via* the two racemic crystalline dihydroxy-acids (V; R′ = R″ = H) which are readily separated by fractional crystallisation. Both *cis*- and *trans*-heptadec-9-enoic acids * have been thus prepared.

The alkoxy-ketone route has yielded oleic and elaidic acids.

An improved method of converting αβ-glycols into the corresponding dibromides by means of hydrogen bromide–acetic acid–sulphuric acid is reported.

As already outlined (*J.*, 1950, 177) our main interest in unsaturated long-chain compounds is to develop a method for their synthesis of the greatest flexibility capable of yielding, in the first instance, both the normal straight-chain mono-olefinic acids and their branched-chain analogues in a pure condition. Although the usual organic techniques, *e.g.*, low-temperature crystallisation, may be used to free the former from contaminants of a similar molecular weight, this is not likely to be possible in the case of the branched-chain materials, which will be obtained as oily mixtures of the possible geometric and stereo-isomers. It was therefore necessary to have available a synthetical route wherein, once the chain was brought into being, the subsequent steps could be carried out quantitatively or, at least, unchanged materials be destroyed before the last stage.

The new ketone synthesis recently described (Bowman, *J.*, 1950, 325) permits the preparation of olefinic acids by way of either alkoxy-ketones (IV; R′ = alkyl) or the corresponding acyloins (IV; R′ = H):

$$\underset{\text{(I.)}}{R'O{\cdot}CHR{\cdot}COCl} + \underset{\text{(II.)}}{(CH_2Ph{\cdot}O_2C)_2CNa{\cdot}[CH_2]_x{\cdot}CO_2{\cdot}CH_2Ph} \longrightarrow \underset{\text{(III.)}}{\begin{matrix}R'O{\cdot}CHR{\cdot}CO\\ \diagup\\ (CH_2Ph{\cdot}O_2C)_2C{\cdot}[CH_2]_x{\cdot}CO_2{\cdot}CH_2Ph\end{matrix}}$$

$$\xrightarrow[(b)\ -2CO_2]{(a)\ H_2-Pd-C} \underset{\text{(IV.)}}{R'O{\cdot}CHR{\cdot}CO{\cdot}[CH_2]_{x+1}{\cdot}CO_2R''} \longrightarrow \underset{\text{(V.)}}{R'O{\cdot}CHR{\cdot}CH(OH){\cdot}[CH_2]_{x+1}{\cdot}CO_2R''}$$

$$\longrightarrow \underset{\text{(VI.)}}{R{\cdot}CHBr{\cdot}CHBr{\cdot}[CH_2]_{x+1}{\cdot}CO_2Et} \longrightarrow \underset{\text{(VII.)}}{R{\cdot}CH{:}CH{\cdot}[CH_2]_{x+1}{\cdot}CO_2H}$$

The practicability of the first route has already been demonstrated (*ibid.*, p. 177) although it was evident that many experimental details required further investigation. A critical examination of both routes has now been carried out to compare their suitability for our purposes. This communication deals with the straight-chain acids, and the results on the branched materials are reported in Part IV (succeeding paper).

First, the preparation of oleic and elaidic acids, both of which have been obtained in a high state of purity by Smith (*J.*, 1939, 974), has been investigated by the alkoxy-ketone route starting from ethyl heptane-1 : 1 : 7-tricarboxylate and 2-methoxydecanoic acid.* The latter is conveniently prepared (Bowman, *loc. cit.*, p. 177) by hydrolysis of the product of interaction of sodium methoxide and methyl 2-bromodecanoate and we have now confirmed its homogeneity by independent synthesis. Carbethoxylation of ethyl methoxyacetate by means of ethyl carbonate in the presence of sodium ethoxide (Wallingford, Hofmeyer, and Jones, *J. Amer. Chem. Soc.*, 1941, **63**, 2057) afforded ethyl methoxymalonate, which on alkylation with *n*-octyl bromide and subsequent hydrolysis and decarboxylation of the reaction product yielded 2-methoxydecanoic acid identical in every respect with the material obtained previously.

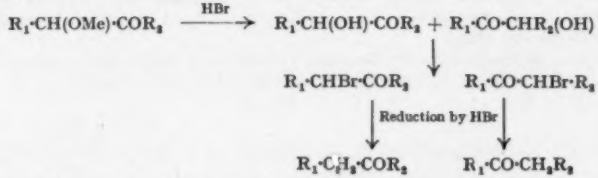
Condensation of 2-methoxydecanoyl chloride (I; R = C_8H_{17}, R′ = Me) with tribenzyl sodioheptane-1 : 1 : 7-tricarboxylate (II; $x = 6$) (Ames, Bowman, and Mason, *J.*, 1950, 174) proceeded normally and gave a keto-ester which on debenzylation, decarboxylation, and

* Geneva convention, $CO_2H = 1$.

subsequent esterification furnished methyl 9-keto-10-methoxyoctadecanoate (IV; R = C_8H_{17}, R′ = R″ = Me, $x = 6$) in 60% yield (almost quantitative when allowance was made for recovery of both starting materials). Ponndorf reduction of the latter with aluminium *iso*propoxide in *iso*propanolic solution in the usual manner furnished ethyl 9-hydroxy-10-methoxyoctadecanoate (V; R = C_8H_{17}, R′ = Me, R″ = Et, $x = 6$), the product being saponified and then re-esterified with ethanol to avoid isolation of mixed esters arising from partial alcoholysis (cf. Owen, *J.*, 1949, 1583). However, this material was not homogeneous and presumably contained some unreduced keto-ester.

In the earlier experiments, the remaining steps (V ⟶ VII) had proved difficult, but since then we became aware of the work of Baudart (*Bull. Soc. chim.*, 1946, **13**, 87) who following Ruzicka, Plattner, and Widmer (*Helv. Chim. Acta*, 1942, **25**, 604, 1086) converted αβ-glycols into the corresponding olefins by treatment with hydrogen bromide in acetic acid (15%) at 90° followed by dehalogenation of the resulting dibromides in acetone solution with zinc dust in the presence of sodium iodide. Application of these techniques to our hydroxy-methoxy-ester gave, first, an impure dibromo-ester, and then an unsaturated ester of iodine value 72 (Calc. : 82). Fractional crystallisation of the derived acids revealed the presence of approximately 10% of stearic acid in addition to oleic and elaidic acids. Similar results were obtained on using high-pressure catalytic hydrogenation in the presence of Raney nickel (Mozingo, *Org. Synth.*, 1941, **21**, 15) in place of the Ponndorf reduction.

Interpretation of these unexpected results was complicated by the uncertainty regarding the purity of the hydroxy-methoxy-ester. Many experiments were carried out to ascertain the source of the stearic acid, but without result. Noteworthy, however, is the reaction of the original 9-keto-10-methoxyoctadecanoic ester with the hydrogen bromide reagent to give a black tar from which, in small yield, a crystalline keto-octadecanoic acid thought to be a mixture of the 9- and the 10-isomer was isolated. A possible mechanism for the formation of these is as follows :



(cf. the reduction of α-bromo-ketones by hydrogen bromide, Kröhnke and Timmler, *Ber.*, 1936, **69**, 614).

A similar product containing approximately the same amount of stearic acid was obtained by starting with the readily purified, higher-melting, *erythro*-9 : 10-dihydroxystearic acid, and applying Baudart's techniques (*loc. cit.*). A sample of the required final product, ethyl 9 : 10-dibromo-octadecanoate, was prepared for comparison by careful bromination of a purified sample of ethyl oleate followed by repeated fractionation of the product under reduced pressure to give material of constant refractive index.

An analogous result is that of Young, Jasaitis, and Levanas (*J. Amer. Chem. Soc.*, 1937, **59**, 403), who obtained *n*-oct-4-ene containing some *n*-octane by treatment of octane-4 : 5-diol with hydrobromic acid in the presence of zinc bromide, followed by debromination of the resulting dibromide with zinc. These workers attributed the presence of the saturated hydrocarbon to the formation of the 4 : 4-dibromo-compound during the first stage, and it may well be that the stearic acid, reported above, arose in a similar manner.

Many variations of the reaction conditions with hydrogen bromide, however, failed to yield a product with either the correct bromine content or the expected refractive index; the use of chromatography was unsuccessful.

The literature on the reaction of αβ-glycols with hydrogen bromide in acetic acid is confusing. Albitski (*J. pr. Chem.*, 1903, **67**, 295) describes the formation of acetoxy-bromo-compounds from dihydroxystearic acids, Baudart (*loc. cit.*) reports (without analyses) the isolation of dibromides, and Hunsdiecker (*Ber.*, 1943, **76**, 142) obtained the corresponding tribromide from aleuritic acid : Ruzicka *et al.* (*loc. cit.*), however, record the necessity for chomatographic purification of dibromides (low yields) prepared with the same reagent. In the macrocyclic field, Stoll, Hulstkamp, and Rouvé (*Helv. Chim. Acta*, 1948, **31**, 543) and Stoll and Commarmont (*ibid.*, p. 1077) obtained acetoxybromo-, or mixtures of this with the corresponding diacetoxy-

compounds, according to the conditions of reaction. Our experiences lead us to conclude that even the prolonged use of a large excess of hydrogen bromide does not bring about complete conversion of αβ-glycols into their dibromides.

Finally, in an attempt to surmount these difficulties, we examined the reaction in the presence of sulphuric acid and at once obtained the required dibromo-acid and thence its ethyl ester in a pure condition; attempts to replace the sulphuric acid by phosphoric acid were unsuccessful. It is noteworthy that, contrary to expectation, the crude dibromo-acid thus obtained was light-coloured, in contrast to that formed in the *absence* of sulphuric acid, which was frequently almost black owing to presence of tar.

Next, the final debromination stage was examined, authentic 9 : 10-dibromooctadecanoic ester being used. The method employing zinc dust in acetone containing sodium iodide (Ruzicka *et al.*, *loc. cit.*) did not give reproducible results, but treatment with activated zinc dust in ethanol (Rollett, *Z. physiol. Chem.*, 1909, **63**, 410; Bloomquist, Holley, and Spencer, *J. Amer. Chem. Soc.*, 1948, **70**, 36; Silberman and Silberman-Martyncewa, *J. Org. Chem.*, 1948, **13**, 707) proved highly satisfactory, furnishing almost quantitative yields of ethyl oleate of theoretical iodine value.

While these experiments were in progress, we also succeeded in effecting reduction of the keto-methoxy-ester (IV; $R = C_8H_{17}$, $R' = R'' = Me$, $x = 6$) catalytically by using Raney nickel W7 (Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 698), the theoretical volume of hydrogen being rapidly taken up to give a quantitative yield of the pure methyl 9-hydroxy-10-methoxyoctadecanoate (V; $R = C_8H_{17}$, $R' = R'' = Me$, $x = 6$). Treatment of the latter with hydrogen bromide–acetic acid–sulphuric acid followed by esterification and passage of the crude ester in light petroleum solution through a short column of activated alumina gave the pure dibromo-octadecanoic ester and thence, by reaction with zinc in ethanol, an unsaturated ester of the required iodine value. Hydrolysis and fractional crystallisation of the resulting acid yielded oleic and elaidic acids, again of the correct iodine value and identical with authentic material; there was no evidence of the presence of saturated contaminants. The oleic acid had a rather low melting point owing, doubtless, to the presence of a small amount of the *trans*-isomer which is difficult to eliminate on the scale employed.

With these methods now available, attention was next directed to the acyloin route as applied to the synthesis of the *cis*- and *trans*-heptadec-9-enoic acids. A somewhat similar route has been used by Ruzicka *et al.* and Baudart (*locc. cit.*), but a circuitous series of reactions was necessary owing to the absence of a direct synthesis of unsymmetrical acyloins. Successive treatment of 2-hydroxynonanoic acid with acetyl chloride and thionyl chloride gave 2-acetoxynonanoyl chloride (I; $R = C_7H_{15}$, $R' = Ac$) which was condensed with tribenzyl sodioheptane-1 : 1 : 7-tricarboxylate as before. Hydrogenolysis, decarboxylation, and deacetylation under *acid* conditions furnished 10-hydroxy-9-ketoheptadecanoic acid (IV; $R = C_7H_{15}$, $R' = R'' = H$, $x = 6$), more conveniently isolated as its ethyl ester (71%). Alkaline hydrolysis could not be used to remove the acetyl group, for King (*J.*, 1936, 1788) has shown that, in alkaline solution, substances of this type are partially isomerised to mixtures of the 10-hydroxy-9-keto- and the 9-hydroxy-10-keto-acids. We have confirmed this isomerisation in the case of 10-hydroxy-9-ketoheptadecanoic acid and isolated a mixture of the two isomers in addition to a small quantity of azelaic acid formed by oxidative fission of the acyloin linkage (cf. King, *loc. cit.*).

Reduction of the acyloin ester was effected catalytically by use of Raney nickel W7 as before, whereas by the Ponndorf method both the acid and its ester were reduced. The latter method is more suitable for acyloins than for alkoxy-ketones, since unreduced material may be readily removed by crystallisation or by oxidative fission in alkaline solution with air or hydrogen peroxide; the catalytic method is, however, more convenient. By either process a mixture of the two stereoisomeric dihydroxy-acids was obtained from which *erythro*-9 : 10-dihydroxyheptadecanoic acid, m. p. 129° (V; $R = C_7H_{15}$, $R' = R'' = H$, $x = 6$) was readily separated by virtue of its sparing solubility in cold ethanol. The more soluble *threo*-isomer, m. p. 86°, was obtained from the mother-liquors. [The assignment of *erythro*- and *threo*-configurations is based on the close analogy to the corresponding dihydroxyoctadecanoic acids, m. p. 129° and 93°, respectively (cf. Bader, *J. Amer. Chem. Soc.*, 1948, **70**, 3938).]

Both compounds were separately treated as before, *i.e.*, with hydrogen bromide–sulphuric acid–acetic acid, followed by zinc in ethanol, to give the pure dibromo-esters and thence the pure *cis*- and *trans*-heptadec-9-enoic acids, respectively.

Our confidence in the purity of the unsaturated acids obtained in the above manner is based on the following considerations. The mechanisms by which αβ-glycols are converted into

olefins *via* the requisite dibromides with aid of hydrogen bromide and zinc have been elucidated by a number of workers, in particular Young, Lucas, Winstein, and their co-workers (*J. Amer. Chem. Soc.*, 1930 *et seq.*), who have shown that the first stage of the reaction is accompanied by a change of configuration at one carbon atom only (Lucas and Wilson, *ibid.*, 1936, **58**, 2396) and that subsequent debromination gives rise to a sterically homogeneous product (Young, Jasaitis, and Levanas, *loc. cit.*). Nevertheless, Campbell, and Eby (*ibid.*, 1941, **63**, 216) have since drawn attention to the work of van Risseghem (*Bull. Soc. chim. Belg.*, 1938, **47**, 194), who demonstrated by means of Raman spectra the presence of the alternative isomer in each *cis*- and *trans*-hex-3-ene obtained from the appropriate dibromide; but as she used a different reagent, *viz.*, phosphorus tribromide, for the preparation of her dibromides, this criticism is not relevant to our substances. In the long-chain field, the debromination of pure *threo*-9 : 10-dibromostearic acid to give oleic acid of the highest purity (m. p. 14°) (Holde and Gorgas, *Z. angew. Chem.*, 1926, **39**, 1443) is further evidence that the last stage occurs in a undirectional manner.

For the heptadec-9-enoic acids synthesised above, the evidence is no less convincing : the *cis*-acid obtained by direct distillation of the crude hydrolysis product of its ester, with no attempt at fractionation beyond rejection of the first drop of distillate, had m. p. 13—13·5° unchanged by further purification including repeated crystallisation of its lithium salt and regeneration therefrom with dilute acid; the crude *trans*-acid, obtained similarly from its ester but without distillation, had m. p. 37—38° raised only to 38° by crystallisation.

In conclusion, it is evident that, although both the alkoxy-ketone and the acyloin route are satisfactory for the synthesis of the straight-chain higher unsaturated acids, yet the latter is superior since it allows the separate preparation of the individual *cis*- and *trans*-isomers. In this connection, it is particularly fortunate that the readily purified, higher-melting *erythro*-dihydroxy-acid gives rise to the more difficultly purified *cis*-acid, which can be thus obtained in a pure state.

The way now appears to be open for the synthesis of many naturally occurring polyunsaturated acids *via* the appropriate polyhydroxy-acids, and experiments in this direction are in progress.

Experimental.

The methods used for the conversion of the malonic ester into the benzyl sodio-ester and the reaction of the latter with the acid chloride were as described by Bowman (*J.*, 1950, 325).

Substituted Keto-acids.—The following modification is a considerable improvement on the original method (*loc. cit.*). A solution of the crude benzyl keto-ester (0·2 mol.) in dry ethyl acetate (400 ml.) was stirred in an atmosphere of hydrogen at room temperature in the presence of anhydrous magnesium sulphate (20 g.) and palladised strontium carbonate (6 g., 10% of Pd) until hydrogenation was complete. The filtered solution (together with ethyl acetate washings) was diluted with dry toluene (250 ml.) and concentrated to about half its volume under reduced pressure to remove water and thus minimise hydrolytic degradation of the acylmalonic acid. The residue was then boiled under reflux for 1 hour to effect decarboxylation and the remaining solvent was then removed mainly at atmosphere pressure and finally *in vacuo*.

Ethyl Methoxymalonate.—Ethyl methoxyacetate (177 g., 1·5 mols.) was added to a suspension of sodium ethoxide (from 34 g. of sodium; 1·5 mols.) in dry, redistilled ethyl carbonate (1250 ml.), and the mixture slowly distilled through a Fenske column until no further distillation of ethanol occurred. The ethyl sodiomethoxymalonate, which separated from the reaction mixture on cooling, was removed by filtration, washed with dry benzene, and decomposed by shaking a suspension of it in benzene with dilute sulphuric acid. The organic layer was separated, washed with water, dried (Na_2SO_4), and distilled to give *ethyl methoxymalonate* as a colourless oil, b. p. 95°/3 mm., n_D^{20} 1·4229 (135 g., 50%) (Found : C, 50·7; H, 8·0. $C_6H_{10}O_5$ requires C, 50·5; H, 7·4%). The diamide, obtained by keeping a portion of the ester for 60 hours with excess of concentrated aqueous ammonia, crystallised from methanol in needles, m. p. 205° (slight decomp.) (Pryde and Williams, *J.*, 1933, 1627, give m. p. 203—204° with slight decomp.).

*Ethyl Methoxy-*n*-octylmalonate.*—Ethyl methoxymalonate (0·1 mol.) was converted into its slightly soluble potassio-derivative by addition to a solution of potassium *tert.*-butoxide (0·1 mol.) in *tert.*-butanol (150 ml.) with stirring, and *n*-octyl bromide (0·1 mol.) added. The mixture was stirred under reflux (bath, 110°) for 8 hours, cooled, and poured into dilute sulphuric acid. The product was isolated in the usual manner and distilled to give, after rejection of a small fore-run, *ethyl methoxy-*n*-octylmalonate* as a colourless oil, b. p. 128°/0·4 mm., n_D^{20} 1·4363 (23 g., 77%) (Found : C, 64·1; H, 10·0. $C_{14}H_{28}O_5$ requires C, 63·6; H, 10·0%).

2-Methoxydecanoic Acid.—The foregoing ester (23 g.) was refluxed for 0·5 hour with sodium hydroxide (120 ml. of 4N.). After addition of water (80 ml.), most of the ethanol was distilled off, and the mixture was then cooled and acidified with sulphuric acid (50 ml. of 20N.); vigorous decarboxylation occurred and the product separated as an oil. The latter was isolated with ether and distilled to give 2-methoxydecanoic acid as a colourless oil, b. p. 130°/1 mm., which rapidly solidified, f. p. 42·5° (thermometer in liquid), identical with a specimen (f. p. 43°) obtained by a different route (Part II, *loc. cit.*).

Methyl 9-*Keto*-10-*Methoxyoctadecanoate* (IV; R = C_8H_{17}, R′ = R″ = Me, x = 6).—Ethyl *n*-heptane-1 : 1 : 7-tricarboxylate (66 g., 0·21 mol.) was converted into the tribenzyl sodio-ester by means of sodium (4·8 g., 0·21 mol.) and benzyl alcohol (68 g., 0·63 mol.) in benzene (350 ml.), and the product treated with 2-methoxydecanoyl chloride (44 g., 0·20 mol.) according to the general procedure. Titration of a sample of the crude benzyl acylmalonate showed the presence of 0·01 equiv. of free acid, corresponding to only 5% of uncombined 2-methoxydecanoic acid. After debenzylation, decarboxylation, and removal of solvent, the residue was shaken with light petroleum (b. p. 40—60°; 350 ml.), the insoluble, viscous heptane-1 : 1 : 7-tricarboxylic acid being removed by washing with 50% aqueous ethanol (2 × 40 ml.) and then water (40 ml.). The dried (Na_2SO_4) petroleum layer was evaporated, and the crude residual acid was converted into the methyl ester by the method of Brown *et al.* (*J. Org. Chem.*, 1947, **12**, 160), chloroform (130 ml.), methanol (100 ml.), and concentrated sulphuric acid (1·5 ml.) being used. Isolation with chloroform in the usual manner, followed by distillation, yielded methyl 2-methoxydecanoate (b. p. 84°/0·5 mm.; 9 g.), an intermediate fraction, and the *ester* as a colourless oil, b. p. 188°/0·5 mm., n_D^{20} 1·4512 (41 g., 60% calculated on the acid chloride but almost quantitative when allowance is made for both the recovered starting materials) (Found: C, 70·1; H, 11·1. $C_{29}H_{52}O_4$ requires C, 70·1; H, 11·2%). In experiments otherwise similar, but omitting use of anhydrous magnesium sulphate and concentration of the solution in the cold before decarboxylation, yields of 50% were obtained.

Ponndorf Reduction of Methyl 9-*Keto*-10-*methoxyoctadecanoate*.—The ester (20 g.) in *iso*propanol (20 ml.) was added during 3 hours to a solution of pure aluminium *iso*propoxide in *iso*propanol (70 ml. of 1N.) being distilled through a Fenske column, and the reaction continued by slow, constant-volume distillations for a further 5 hours. Hydrolysis of the ester and decomposition of the aluminium complex were effected by addition of sodium hydroxide solution (150 ml. of 2N.), refluxing the mixture for 1 hour, and removing the *iso*propanol by distillation. After acidification, the products were isolated with benzene, the organic layer being concentrated to about 100 ml. and subjected to azeotropic esterification with ethanol (50 ml.) and concentrated sulphuric acid (0·5 ml.). Isolation of the ester in the usual manner, followed by distillation, furnished impure *ethyl* 9-*hydroxy*-10-*methoxyoctadecanoate* (17 g.), b. p. 185—190°/0·1 mm., n_D^{20} 1·4536 (Found: C, 70·6; H, 11·9. $C_{21}H_{42}O_4$ requires C, 70·3; H, 11·8%).

Reaction with Hydrogen Bromide in Acetic Acid.—Treatment of the foregoing ester (16 g.) with hydrogen bromide in acetic acid (300 ml.; *d* 1·2) at 90—100° for 40 hours, followed by removal of volatile acids *in vacuo*, furnished a tarry product which was triturated with light petroleum (b. p. 40—60°). The filtered extract was evaporated, the residue esterified azeotropically, and the resulting impure ethyl 9 : 10-dibromoctadecanoate distilled as a yellow oil, n_D^{20} 1·4771 (18 g.) (Found: C, 53·4; H, 8·7. Calc. for $C_{20}H_{38}O_2Br_2$: C, 51·1; H, 8·2%).

Ethyl threo-9 : 10-*Dibromoctadecanoate*.—Commercial oleic acid was crystallised from acetone at −30°, and stearic acid removed by crystallisation at −20° (Smith, *loc. cit.*). The resulting yellow oil was esterified azeotropically, and the crude, undistilled ester (14 g.) in dry ether (200 ml.) at −15° to −20° was treated with bromine (7·5 g.) with stirring. Addition was completed in 10 minutes, and the mixture was warmed to room temperature, washed with water, and dried (Na_2SO_4). Distillation yielded a small fore-run and then the bromo-ester (14 g.), b. p. 195—200°/0·1 mm., n_D^{20} 1·4861. After two redistillations, the product had n_D^{20} 1·4871, unchanged by further fractionation.

Debromination of the Impure Synthetic Dibromo-ester.—The dibromo-ester (17 g.; from hydrogen bromide treatment of the Ponndorf reduction product) was refluxed for 3 hours with zinc (25 g.), sodium iodide (34 g.), and acetone (400 ml.), the filtered solution being concentrated under reduced pressure and diluted with water. The unsaturated ester was isolated with light petroleum (b. p. 60—80°) and distilled as a colourless oil, b. p. 157—160°/0·1 mm. (I.V., 72·1. Calc. for $C_{20}H_{38}O_2$: I.V., 82·0). Saponification in the usual manner, followed by fractional crystallisation from acetone at progressively lower temperatures, yielded stearic acid (m. p. and mixed m. p. 69—70°), elaidic acid (m. p. and mixed m. p. 43·5°; *p*-phenylphenacyl ester, m. p. and mixed m. p. 73—74°), and oleic acid, isolated as the lithium salt, which was directly converted into *p*-phenylphenacyl oleate (m. p. and mixed m. p. 60°).

Reaction of 9-*Keto*-10-*methoxyoctadecanoic Acid with Hydrogen Bromide in Acetic Acid*.—The acid (from saponification of 5 g. of methyl ester) was heated with hydrogen bromide in acetic acid under the same conditions as used previously with the hydroxy-methoxy-compound. After removal of volatile acids as previously, the residual brown viscous material was repeatedly extracted with boiling light petroleum (b. p. 60—80°), leaving a residue which was still acidic since it readily dissolved in aqueous alkali. Attempts to purify it either by low-temperature crystallisation from ethyl acetate, in which it is readily soluble, or by distillation of the ethyl ester (not volatile at 300°/0·5 mm.) were unsuccessful. Evaporation of the light petroleum extracts furnished a crystalline residue, which separated from acetone (charcoal) at −70° in small plates, m. p. 72° (1·2 g.). Recrystallisation from light petroleum (b. p. 60—80°) yielded a material, m. p. 73—74° (Found: C, 72·5; H, 11·5. Calc. for keto-octadecanoic acids, $C_{18}H_{34}O_3$: C, 72·4; H, 11·5%), which was recovered unchanged, m. p. and mixed m. p. 73°, after being warmed with a solution of chromic acid in acetic acid, and after attempted catalytic hydrogenation in ethyl acetate solution in the presence of palladised strontium carbonate. Reduction by the modified Wolff–Kishner method, exactly as described by Huang-Minlon (*loc. cit.*), gave stearic acid, plates (from acetone), m. p. 68° undepressed by admixture with an authentic specimen.

Catalytic Hydrogenation of Methyl 9-*Keto*-10-*methoxyoctadecanoate*.—(a) *Using Raney nickel*. A solution of the ester (12 g.) in methanol (100 ml.) was stirred with Raney nickel (Mozingo, *loc. cit.*) in hydrogen (50 atm.; 100—110°) for 18 hours. The filtered solution was distilled to give crude methyl 9-hydroxy-10-methoxyoctadecanoate as a colourless oil, b. p. 190°/0·5 mm., n_D^{20} 1·4551 (9 g.). The analytical results (Found: C, 70·6; H, 12·0. Calc. for $C_{20}H_{40}O_4$: C, 69·7; H, 11·7%) suggest that side reactions involving loss of oxygen had occurred. This material was converted by the procedures already used for the ethyl ester into the crude dibromo-ester and thence into the corresponding

unsaturated ester (I.V., 70·2). Saponification yielded a mixture of acids which were separated as before into stearic, elaidic, and oleic acids.

(b) *Using Raney nickel* W7. The ester (15·5 g.) was added to Raney nickel W7 catalyst (*ca.* 5 g.; Adkins and Billica, *loc. cit.*) previously stirred under hydrogen with ethanol (250 ml.). Absorption was rapid and ceased when 1000 ml. had been taken up (theory, 1010 ml.). After the catalyst had been filtered off and washed with ethanol, the combined filtrates were concentrated to small bulk under reduced pressure, and then light petroleum (b. p. 60—80°; 150 ml.) was added. The solution was washed with dilute sulphuric acid, potassium hydrogen carbonate solution, and water, then dried (Na_2SO_4) and distilled. The pure *methyl 9-hydroxy-10-methoxyoctadecanoate* was thus obtained as a colourless oil, b. p. 178°/0·5 mm. (14 g.), n_D^{20} 1·4553 (Found : C, 70·0; H, 11·9. $C_{20}H_{40}O_4$ requires C, 69·7; H, 11·7%).

Model Experiments with erythro-9 : 10-*Dihydroxyoctadecanoic Acid.*—(1) *With hydrogen bromide in acetic acid.* (i) The dihydroxy-acid (4 g.; m. p. 130°) was warmed with the reagent (40 ml.; *d* 1·2) to 90° during 3 hours and then kept at this temperature for a further 12 hours, whereafter the products were isolated and esterified as before. Distillation yielded the following fractions : (*a*) b. p. 180—192°/0·2 mm., n_D^{20} 1·4787 (0·5 g.), (*b*) b. p. 192—197°/0·2 mm., n_D^{20} 1·4823 (1·5 g.), and (*c*) b. p. 197—198°/0·2 mm., n_D^{20} 1·4853 (0·5 g.). Comparison of these refractive indices with that of the pure product (n_D^{20} 1·4871) obtained from ethyl oleate and bromine, shows that even the highest-boiling fraction (*c*) contains much impurity. A solution of the combined fractions in light petroleum (b. p. 40—60°; 150 ml.) was run on a 6″ column of activated alumina, and elution effected with the same solvent (200 ml.), but only slight separation was realised, the fractions having n_D^{20} 1·4818—1·4842.

(ii) A sample of the hydroxy-acid (7 g.) was treated with hydrogen bromide as above for 40 hours at 100°; a portion of the light petroleum-soluble dibromo-acid was dried to constant weight *in vacuo* and analysed (Found : Br, 34·1. Calc. for $C_{18}H_{34}O_3Br_2$: Br, 36·2%). The remainder was converted into ester (9 g.; n_D^{20} 1·4832), which was then debrominated by the zinc–sodium iodide–acetone method to give an unsaturated ester (I.V. 72). Saponification, followed by crystallisation of the resulting acid from light petroleum (b. p. 40—60°) at 0°, yielded stearic acid, m. p. 68—69° and mixed m. p. 69—70° (0·05 g. from 1·5 g. of the unsaturated ester).

(2) *With hydrogen bromide–acetic acid–sulphuric acid.* To the dihydroxy-acid (5 g.) was added hydrogen bromide–acetic acid (50 ml.; *d* 1·25), followed by concentrated sulphuric acid (5 ml.) in small portions with shaking and cooling. The solid had completely dissolved in a few hours, but after 16 hours a small layer of oil separated; the mixture was then heated at 100° for 8 hours (a further 5 ml. of the hydrogen bromide reagent were added after 4 hours). Water was then added, and the pale-red oil isolated with light petroleum (b. p. 60—80°). After being washed with water and dried ($MgSO_4$), the solvent was removed, and the residue esterified azeotropically. The crude ester was dissolved in light petroleum (b. p. 40—60°; 200 ml.), run on a 6″ column of activated alumina, and eluted with the same solvent (400 ml.). Distillation of the colourless total eluates yielded ethyl *threo*-9 : 10-dibromoctadecanoate as a pale yellow oil, b. p. 210°/0·3 mm., n_D^{20} 1·4866 (6·5 g.) (Found : C, 51·5; H, 8·3; Br, 34·1. Calc. for $C_{20}H_{38}O_2Br_2$: C, 51·1; H, 8·2; Br, 34·0%). If the purification using alumina was omitted, some decomposition occurred on distillation.

Zinc (15 g.) was activated by 5 minutes' boiling with ethanol (75 ml.) and aqueous hydrobromic acid (1 ml. of 60%), and after addition of the foregoing dibromo-ester (6·5 g.), the mixture was refluxed for 1 hour in an atmosphere of nitrogen. The zinc was removed by filtration and washed with light petroleum (b. p. 60—80°; 100 ml.), and the combined filtrates were washed with dilute sulphuric acid and then water. After drying ($MgSO_4$), the solution was distilled (nitrogen leak) to give ethyl oleate as a colourless oil, b. p. 148°/0·4 mm., n_D^{20} 1·4516 (3·4 g.) (I.V., 81·9. Calc. : I.V., 82·0). When the ester was saponified (in nitrogen) in the usual manner, the oleic acid (b. p. 160°/0·1 mm.) obtained had m. p. 12° (capillary) [α-form has m. p. 13·36° according to Smith (*loc. cit.*)], n_D^{20} 1·4608, I.V., 90·0 (Calc. for $C_{18}H_{34}O_2$: I.V., 89·9). The low m. p. is attributed to the presence of isomeric octadecenoic acids in the sample of oleic acid used as starting material.

Comparison of Debromination Methods.—(a) *Use of zinc–sodium iodide.* The substantially pure ethyl *threo*-dibromoctadecanoate (obtained from ethyl oleate, see p. 1083) was debrominated by the method described on p. 1083 to give ethyl oleate (b. p. 148—150°/0·1 mm.) having I.V. 78·2 (theory, 82·0) although no bromine was present.

(b) *Use of activated zinc in ethanol.* When the same sample of dibromo-ester was debrominated by use of activated zinc as above, the ethyl oleate produced (b. p. 150—152°/0·1 mm.) had I.V. 82·6.

Synthetic Ethyl 9 : 10-*Dibromoctadecanoate.*—Methyl 9-hydroxy-10-methoxyoctadecanoate (obtained by using Raney nickel W7; 9 g.) was treated with hydrogen bromide–acetic acid reagent (100 ml.) in the presence of sulphuric acid (25 ml.) as previously. Esterification of the crude product followed by passage through alumina furnished ethyl 9 : 10-dibromoctadecanoate (*erythro-* and *threo*-isomers) as an almost colourless oil, b. p. 200°/0·3 mm., n_D^{20} 1·4870 (9 g., 73%).

Oleic and Elaidic Acids.—Debromination of the latter ester (13 g.) by means of activated zinc yielded a mixture of ethyl oleate and elaidate as a colourless oil, b. p. 155°/0·2 mm., n_D^{20} 1·4513 (7·5 g.) (Found : I.V., 81·4. Calc. for $C_{20}H_{38}O_2$: I.V., 82·0). Saponification in the usual manner furnished a mixture of acids separated by low-temperature crystallisation from acetone into elaidic acid (1·9 g.; crude) and oleic acid (isolated as the lithium salt; 1·5 g.). The elaidic acid separated from light petroleum (b. p. 40—60°) in large rectangular plates, m. p. and mixed m. p. 44—44·5° (capillary) (Smith, *loc. cit.*, gives 43·5—44·5°, capillary) (Found : I.V., 88·3, 88·4. Calc. : 89·9). Lithium oleate separated from ethanol in plates, m. p. 196°. This salt (1·5 g.) was shaken with ethanol-free ether (100 ml.) and dilute hydrochloric acid (100 ml. of 2N.) until all solid had dissolved. Light petroleum (b. p. 60—80°; 100 ml.) was added, and after being washed with water and dried (Na_2SO_4), the oleic acid was distilled as a colourless

oil, b. p. 165°/0·4 mm., n_D^{20} 1·4596, m. p. 11·5° (capillary) [α-form, 13·36° (thermometer in liquid); Smith, *loc. cit.*] undepressed by admixture with the natural product (Found: I.V., 89·3. Calc.: 89·9).

A portion of the elaidic acid (0·5 g.) in ethyl acetate (40 ml.) was shaken in hydrogen with palladised strontium carbonate (0·5 g. of 10%) and the stearic acid resulting from evaporation of the filtered solution was crystallised once from acetone, separating in plates, m. p. and mixed m. p. 70·5°.

Ethyl 2-Bromononanoate.—A sample of commercial pelargonic acid was converted into its ester azeotropically, and the product fractionated through a Fenske column (total-reflux head), the fraction, b. p. 105—107°/10 mm., being collected. Saponification and distillation yielded nonanoic acid, b. p. 126°/2 mm., f. p. 12° (thermometer in liquid). Thionyl chloride (240 ml.) was added to the foregoing acid (126 g.) and, after being kept at 30° for 1 hour, the mixture was heated at 100° for 1 hour and then at 110° for 3 hours while bromine (135 g.) was added. After refluxing for a further 3 hours the mass was set aside overnight, and, when excess of thionyl halides had been removed by distillation *in vacuo*, was poured into ethanol (400 ml.). The resulting clear yellow solution was kept at room temperature for 3 hours and then diluted with water (1 l.), the product being isolated with chloroform (cf. Schwenk and Papa, *J. Amer. Chem. Soc.*, 1948, **70**, 3627). Distillation through a Vigreux column afforded ethyl 2-bromononanoate as a colourless oil, b. p. 87—89°/1 mm., n_D^{20} 1·4530 (193 g., 91%).

2-Hydroxynonanoic Acid.—(*a*) The foregoing ester (193 g.) was added to a solution of potassium acetate (290 g.) in glacial acetic acid (400 ml.), and the mixture stirred under reflux for 7 hours (bath 180°) (cf. Mendel and Coops, *Rec. Trav. chim.*, 1939, **58**, 1133). After removal of acetic acid (200 ml.) by distillation, water (800 ml.) was added and the products were isolated with benzene (2 × 150 ml.). Evaporation yielded an oil, which was dissolved in ethanol (150 ml.) and refluxed for 0·5 hour with sodium hydroxide solution (200 ml.; 10N.) whereafter water (600 ml.) was added and most of the ethanol removed by distillation before the solution was acidified with sulphuric acid (600 ml.; 5N.). The crude product, which crystallised on cooling, was removed by filtration and washed with water (2 × 100 ml.), some oily material being removed with the filtrate. The damp solid was dissolved in benzene–ethyl acetate (1200 ml.; 3 : 1 by vol.) and, after being washed with water, the solution was dried (Na_2SO_4) and evaporated under reduced pressure. Crystallisation of the residue from light petroleum (b. p. 60—80°; 600 ml.) yielded 2 hydroxynonanoic acid (87 g.), m. p. 70°. A further crop (4 g.; m. p. 70°) was obtained by concentration of the mother-liquors (total yield 65% on the nonanoic acid). The acid was crystallised from light petroleum (b. p. 60—80°), giving lustrous plates, m. p. 70·5° unchanged by further crystallisation from light petroleum and chloroform (Found: C, 62·2; H, 10·3. Calc. for $C_9H_{18}O_3$: C, 62·1; H, 10·4%). The *p-bromophenacyl* ester separated from ethanol in colourless leaflets, m. p. 95·5° (Found: C, 55·5; H, 6·0. $C_{17}H_{23}O_4Br$ requires C, 55·0; H, 6·2%).

(*b*) In another experiment on the same scale, the crude α-bromo-acid chloride, obtained by removal of the thionyl halides as before, was mixed with acetic acid (250 ml.), and then formic acid (150 ml. of 98%) was added during 50 minutes with gentle warming. The mixture was kept at 100° for 1 hour and after removal of formic and acetic acids *in vacuo*, sodium hydroxide solution (1250 ml.; 2N.) and dioxan (100 ml.) were added. After 1 hours' refluxing, more sodium hydroxide solution (120 ml.) was added, and the solution refluxed for a further 7 hours. Dioxan (200 ml.) and sulphuric acid (500 ml., 10N.) were added with cooling but the hydroxy-acid did not crystallise and was therefore extracted with light petroleum (b. p. 40—60°)–ethyl acetate (750 ml.; 4 : 1). The combined extracts were washed with water, dried (Na_2SO_4), and evaporated as previously. Crystallisation of the residue from light petroleum (b. p. 60—80°) yielded a total of 91 g. of 2-hydroxynonanoic acid, m. p. 70° (65% on the nonanoic acid).

2-Acetoxynonanoyl Chloride.—A mixture of acetyl chloride (75 ml.) and the foregoing acid (50 g.) was set aside at room temperature for 2 hours, excess of acetyl chloride removed *in vacuo*, and thionyl chloride (50 ml.) added. After being warmed at 40° for 1·5 hours and then at 60° for a similar period, the mixture was distilled to give the *acid chloride* as a colourless oil, b. p. 94°/0·5 mm. (53 g.) (Found: Cl, 15·3. $C_{11}H_{19}O_3Cl$ requires Cl, 15·1%).

10-Hydroxy-9-ketoheptadecanoic Acid (IV; R = C_7H_{15}, R′ = R″ = H, x = 6).—The foregoing acid chloride (47 g., 0·2 mol.) was condensed with tribenzyl sodioheptane-1 : 1 : 7-tricarboxylate (0·21 mol.), and the product hydrogenated and decarboxylated, as in the previous example. The crude acetoxy-ketone was shaken with light petroleum (b. p. 40—60°; 350 ml.) and aqueous ethanol (3 × 40 ml. of 50%), forming a three-phase system from which the lowest, aqueous layer, containing heptane-1 : 1 : 7-tricarboxylic acid, was separated on each occasion. Removal of the solvent from the combined upper and middle layers furnished an oil, which was dissolved in ethanol (350 ml.) and refluxed for 3 hours with sulphuric acid (250 ml. of 2N.). Water was then added to the cooled mixture and the products were isolated with benzene. Crystallisation from light petroleum (b. p. 40—60°; 350 ml.) at 0° yielded the *acid* (8 g.), which separated from light petroleum (b. p. 60—80°) –ethyl acetate (200 : 80 ml.) in plates, m. p. 72·5° (Found: C, 68·0; H, 10·6. $C_{17}H_{32}O_4$ requires C, 68·0; H, 10·7%). By evaporation of the mother-liquors, refluxing of the residue with ethanol–sulphuric acid for 20 hours, and isolation as before, a further crop of the acid (10 g.) was obtained (total yield 18 g.; 30% on the acid chloride).

Ethyl 10-Hydroxy-9-ketoheptadecanoate.—The mother-liquors from the crystallisation of the foregoing acid were evaporated, and the residual mixed acids esterified azeotropically with ethanol (100 ml.), benzene (150 ml.), and sulphuric acid (0·5 ml.). Isolation with benzene followed by fractional distillation of the esters yielded crude ethyl 2-hydroxynonanoate and *ethyl 10-hydroxy-9-ketoheptadecanoate* (16 g., 25%) as a pale yellow oil, b. p. 184°/0·3 mm., which rapidly solidified and then separated from light petroleum (b. p. 40—60°) at −15° in plates, m. p. 32·5° (Found: C, 69·6; H, 10·9. $C_{19}H_{36}O_4$ requires C, 69·4; H, 11·0%). In a later series of experiments on the same scale, ethanol (200 ml.) and concentrated sulphuric acid (1 ml.) were added to the benzene solution obtained from the ethanol–sulphuric acid treatment, and this mixture was esterified azeotropically to give the hydroxy-keto-ester in improved yield (47 g., 71%).

Partial Isomerisation of 10-*Hydroxy*-9-*ketoheptadecanoic Acid.*—The acid (0·5 g.), dissolved in ethanol, (30 ml.), was refluxed in an atmosphere of commercial nitrogen with sodium hydroxide solution (10 ml. 2N.) for 0·5 hour. After addition of water (40 ml.), most of the ethanol was removed by distillation, and the residue acidified with sulphuric acid (15 ml.; 4N.), the resulting solid being collected by filtration. Crystallisation from light petroleum (b. p. 60—80°)–ethyl acetate furnished a small quantity of azelaic acid (m. p. 105°, undepressed on admixture with an authentic specimen), and evaporation of the mother-liquors, followed by crystallisation of the residue from light petroleum (b. p. 60—80°), yielded the equilibrium mixture of 10-hydroxy-9-keto- and 9-hydroxy-10-keto-heptadecanoic acids as plates, m. p. 61° (Found: C, 67·9; H, 10·7%).

The 9 : 10-*Dihydroxyheptadecanoic Acids.*—(*a*) When 10-hydroxy-9-ketoheptadecanoic acid (15 g.), dissolved in *iso*propanol (180 ml.), was added to a solution of aluminium *iso*propoxide in *iso*propanol (120 ml., 1M.) a large amount of solid separated, but gradual reduction was effected by slow distillation through a Fenske column fitted with a reflux head. After 1 hour, xylene (100 ml.) was added but the solid did not dissolve and the distillation was therefore resumed. When no further distillation of acetone occurred (10 hours), most of the remaining *iso*propanol was removed by distillation. Sulphuric acid (200 ml.; 5N.) was added to the residue, and the xylene removed by steam-distillation. The oily product solidified on cooling and was filtered off. Entrained inorganic materials were removed by boiling with water and, after cooling, the product was again filtered off. Crystallisation from ethanol (100 ml.), evaporation of the filtrate, and crystallisation of the residue from ethanol–ethyl acetate (80 ml.; 1 : 1) furnished erythro-9 : 10-*dihydroxyheptadecanoic acid* (6·4 g.), which separated from ethanol–ethyl acetate in plates, m. p. 128—129°, unchanged by further crystallisation (Found: C, 67·9; H, 10·9. $C_{17}H_{34}O_4$ requires C, 67·5; H, 11·3%). The *ethyl* ester, prepared by the azeotropic method, separated from light petroleum (b. p. 60—80°) in plates, m. p. 98·5° (Found: C, 69·3; H, 11·6. $C_{19}H_{38}O_4$ requires C, 69·1; H, 11·6%).

The ethyl acetate–ethanol mother-liquors from which the above acid had been crystallised were evaporated to dryness *in vacuo*. Crystallisation of the residue from ethyl acetate afforded a material, m. p. 80—90° (3·6 g.). Fractional crystallisation from ethyl acetate furnished threo-9 : 10-*dihydroxyheptadecanoic acid*, m. p. 85—86° (Found: C, 67·4; H, 10·8%). Alternatively, ethyl 10-hydroxy-9-ketoheptadecanoate (16 g.) was reduced in exactly the same manner as for methyl 9-keto-10-methoxyoctadecanoate, and the acids were separated as above to give the *erythro*- (6·6 g.) and *threo*-acids (3·6 g.).

(*b*) A solution of ethyl 10-hydroxy-9-ketoheptadecanoate (25 g.) in ethanol (200 ml.) was hydrogenated at normal pressure and temperature in the presence of Raney nickel W7 catalyst (*ca.* 5 g.), absorption being complete in 8 hours when 1670 ml. had been taken up (theory, 1710 ml.). Saponification and fractional crystallisation as in the previous case yielded the isomeric dihydroxy-acids in approximately the same proportions.

cis-*Heptadec*-9-*enoic Acid.*—*erythro*-9 : 10-Dihydroxyheptadecanoic acid (7 g.) was treated with hydrogen bromide and acetic–sulphuric acids, and the crude reaction product esterified exactly as for the corresponding stearic acid derivative. *Ethyl* threo-9 : 10-*dibromoheptadecanoate* was thus obtained as a pale yellow oil, b. p. 208°/0·5 mm., n_D^{20} 1·4871 (Found: C, 49·9; H, 7·9; Br, 34·9. $C_{19}H_{36}O_2Br_2$ requires C, 50·0; H, 8·0; Br, 35·0%). This ester (7 g.) was then treated with activated zinc in ethanol as before and furnished *ethyl* cis-*heptadec*-9-*enoate* (4·5 g.), a colourless oil, b. p. 139°/0·1 mm., n_D^{20} 1·4507 (Found: C, 77·2; H, 12·5%; I.V., 86·6. $C_{19}H_{36}O_2$ requires C, 77·0; H, 12·2%; I.V., 85·6).

Hydrolysis of the latter ester (4 g.) in an atmosphere of nitrogen furnished cis-*heptadec*-9-*enoic acid* as a colourless oil, b. p. 175°/0·5 mm., n_D^{20} 1·4598, m. p. 13—13·5° (capillary) (Found: C, 76·2; H, 12·2%; I.V., 95·3. $C_{17}H_{32}O_2$ requires C, 76·1; H, 12·0%; I.V., 94·6). The *lithium* salt separated from ethanol in rectangular plates, m. p. 198° (Found: C, 74·0; H, 11·5. $C_{17}H_{31}O_2Li$ requires C, 74·4; H, 11·4%). The p-*phenylphenacyl* ester, prepared directly from the lithium salt, crystallised from light petroleum (b. p. 60—80°) at −15° in plates, m. p. 61—62° (Found: C, 80·5; H, 9·2. $C_{31}H_{42}O_3$ requires C, 80·5; H, 9·2%).

A sample of the free acid (0·25 g.) in ethyl acetate (25 ml.) was shaken with palladised strontium carbonate (0·2 g. of 10%) in hydrogen for 4 hours. The filtered solution was evaporated to dryness, and the residual heptadecanoic acid crystallised from light petroleum (b. p. 60—80°), from which it separated in lustrous plates, m. p. 62—63° (lit., 61°).

trans-*Heptadec*-9-*enoic Acid.*—*threo*-9 : 10-Dihydroxyheptadecanoic acid (2·5 g.) was treated with hydrogen bromide–acetic acid–sulphuric acid as in the previous cases to give *ethyl* erythro-9 : 10-*dibromoheptadecanoate* as an almost colourless oil, b. p. 202°/0·4 mm., n_D^{20} 1·4876 (2·5 g.) (Found: C, 49·8; H, 8·4. $C_{19}H_{36}O_2Br_2$ requires C, 50·0; H, 8·0%). Debromination with activated zinc yielded *ethyl* trans-*heptadec*-9-*enoate* as a colourless oil, b. p. 150°/0·5 mm., n_D^{20} 1·4499 (1·5 g.) (Found: C, 77·2; H, 12·0%; I.V., 85·7. $C_{19}H_{36}O_2$ requires C, 77·0; H, 12·2%; I.V., 85·6). By saponification in the usual manner, trans-*heptadec*-9-*enoic acid* was obtained by isolation with light petroleum (b. p. 60—80°). A portion of the residue, dried *in vacuo*, had m. p. 37—38° (showing absence of any significant amount of the *cis*-isomer) raised to 38° by crystallisation from light petroleum (b. p. 40—60°) at −5° (Found: C, 76·1; H, 12·1%; I.V., 95·2. $C_{17}H_{32}O_2$ requires C, 76·1; H, 12·0%; I.V., 94·6). The p-*phenylphenacyl* ester separated from acetone at 0° in large rectangular plates, m. p. 74—75° (Found: C, 80·2; H, 9·4. $C_{31}H_{42}O_3$ requires C, 80·5; H, 9·2%).

The authors thank the Medical Research Council for a grant which enabled one of them (D. E. A.) to participate in this work, and also Dr. H. N. Rydon for his generous assistance in this matter.

BIRKBECK COLLEGE, LONDON, E.C.4. [*Received, December 6th*, 1950.]

239. *Synthetic Long-chain Aliphatic Compounds. Part IV. Some Methyl-substituted Oleic Acids.*

By D. E. Ames and R. E. Bowman.

Further applications of the alkoxy-ketone unsaturated acid synthesis (see Part III, preceding paper) have yielded 12-methyl- and 5 : 7 : 13 : 17-tetramethyl-octadec-9-enoic acids * of high purity. An attempt to use the acyloin route for the preparation of 7 : 11-dimethyloctadec-9-enoic acid failed, and the former route is thus to be preferred for the synthesis of branched-chain unsaturated acids. Preliminary experiments on the synthesis of olefinic acids bearing an alkyl group on the double bond have yielded 9-methyloctadec-9-enoic acid of moderate purity.

As described in Part III (preceding paper), efficient methods have now been developed for the synthesis of straight-chain unsaturated acids from either α-alkoxy-ketones or acyloins. The experiments now described were undertaken to examine the suitability of both methods for the preparation of the branched-chain analogues of oleic acid. No particular significance, however, is to be attributed to the choice of final products, which have been chosen primarily from the point of view of ease of preparation of starting materials.

The alkoxy-ketone route was first applied to the synthesis of a mono- and a tetra-methyloleic acid. 4-Methyldecanoic acid,* obtained from *n*-hexylmagnesium bromide and ethyl lævulate (Cason *et al.*, *J. Amer. Chem. Soc.*, 1944, **66**, 1764), was converted *via* the α-bromo-ester into 2-methoxy-4-methyldecanoic acid (I) in the manner used for the preparation of the unmethylated acid (Bowman, *J.*, 1950, 175). The acid chloride from (I) and ethyl heptane-1 : 1 : 7-tricarboxylate were then subjected to the debenzylation ketone synthesis to give 9-keto-10-methoxy-12-methyloctadecanoic acid, isolated as its ethyl ester (II) in 45% yield.

$CH_3 \cdot [CH_2]_5 \cdot CHMe \cdot CH_2 \cdot CH(OMe) \cdot CO_2H$ (I.) $\quad CH_3 \cdot [CH_2]_5 \cdot CHMe \cdot CH_2 \cdot CH(OMe) \cdot CO \cdot [CH_2]_7 \cdot CO_2Et$ (II.)

Catalytic reduction of (II) by means of Raney nickel W7 at room temperature and pressure in ethanol readily gave the pure hydroxy-methoxy-ester, converted by hydrogen bromide–acetic acid–sulphuric acid followed by esterification into the corresponding dibromo-ester. Debromination of the latter with zinc and ethanol then gave the unsaturated ester, which was hydrolysed to give an oily product consisting of the *cis*- and *trans*-12-methyloctadec-9-enoic acids (III); both ester and derived acid had almost the theoretical iodine values.

$CH_3 \cdot [CH_2]_5 \cdot CHMe \cdot CH_2 \cdot CH{:}CH \cdot [CH_2]_7 \cdot CO_2H$ (III.)

$CH_3 \cdot CHMe \cdot [CH_2]_9 \cdot CHMe \cdot [CH_2]_3 \cdot CH(OEt) \cdot CO_2H$ (IV.)

The intermediates chosen for the second acid (VIII) were (IV) and (VI). The former was readily obtained by the usual malonic ester synthesis employing dihydrocitronellyl bromide and potassio-ethoxymalonic ester, and the latter from the readily accessible ethyl 7-keto-5-methyloctanoate (V) (Ames and Bowman, *J.*, 1950, 329) in the following manner:

$$CH_3 \cdot CO \cdot CH_2 \cdot CHMe \cdot [CH_2]_3 \cdot CO_2Et \text{ (V.)} \xrightarrow[(b)\ H_2\text{–Pd}]{(a)\ CN \cdot CH_2 \cdot CO_2Et} CN \cdot CH(CO_2Et) \cdot CHMe \cdot CH_2 \cdot CHMe \cdot [CH_2]_3 \cdot CO_2Et$$

$$\xrightarrow{\text{Alcoholysis}} CH(CO_2Et)_2 \cdot CHMe \cdot CH_2 \cdot CHMe \cdot [CH_2]_3 \cdot CO_2Et \text{ (VI.)}$$

Thionyl chloride converted (IV) into the acid chloride, which on reaction with the tribenzyl sodio-derivative of (VI) gave a keto-ester which on debenzylation and decarboxylation furnished the ethoxy-keto-acid, isolated as its ethyl ester (VIII); the yield (29%), however, was the lowest yet encountered in this synthesis and is attributed to difficulties in completing the ester-interchange of (VI) with benzyl alcohol owing to steric factors.

* Geneva numbering, $CO_2H = 1$.

The ester (VII) then yielded, by way of the usual stages (reduction, conversion into dibromides, debromination, and hydrolysis), an oily mixture of the stereoisomers of *cis*- and *trans*-5 : 7 : 13 : 17-tetramethyloctadec-9-enoic acids (VIII); again, the product was exceptionally pure as judged by its nearly theoretical iodine value. A sample of the corresponding saturated acid was also prepared by catalytic hydrogenation of (VIII).

$CH_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CH(OEt){\cdot}CO{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CO_2Et$
(VII.)

$CH_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CH{:}CH{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CHMe{\cdot}[CH_2]_3{\cdot}CO_2H$
(VIII.)

Attention was next directed to the use of the acyloin synthesis for the preparation of 7 : 11-dimethyloctadec-9-enoic acid. Heptyl methyl ketone was converted by reaction with cyanoacetic ester and hydrogenation of the product (Cope *et al.*, *J. Amer. Chem. Soc.*, 1941, **63**, 3452), followed by hydrolysis and decarboxylation, into 3-methyldecanoic acid (IX). Bromination by Papa and Schwenk's method (*ibid.*, 1948, **70**, 3627) gave the α-bromo-acid, and reaction with potassium acetate and hydrolysis with alkali afforded crude 2-hydroxy-3-methyldecanoic acid; this separated as a gel from light petroleum at low temperatures, and was purified by careful vacuum-fractionation of its ethyl ester through a Fenske column. Hydrolysis furnished an oily acid, converted by successive treatment with acetyl chloride and thionyl chloride into the acetoxy-acid chloride (X).

$CH_3{\cdot}[CH_2]_6{\cdot}CHMe{\cdot}CH_2{\cdot}CO_2H$
(IX.)

$CH_3{\cdot}[CH_2]_6{\cdot}CHMe{\cdot}CH(OAc){\cdot}COCl$
(X.)

The requisite malonic ester (XII) was next prepared by starting from trimethylene glycol :

$$HO{\cdot}[CH_2]_3{\cdot}OH \xrightarrow{S_2Cl_2} HO{\cdot}[CH_2]_3Cl \xrightarrow[(2)\ HBr\text{–}HOAc\text{–}H_2SO_4]{(1)\ \text{Malonation}} Br{\cdot}[CH_2]_4{\cdot}CO_2H \xrightarrow[(3)\ \text{Hydrolysis}]{(1)\ \text{Esterification}\ (2)\ CH_3{\cdot}CO{\cdot}CHNa{\cdot}CO_2Et}$$

$$CH_3{\cdot}CO{\cdot}[CH_2]_5{\cdot}CO_2Et \xrightarrow[(b)\ H_2\text{–}Pd\ (c)\ \text{Alcoholysis}]{(a)\ CN{\cdot}CH_2{\cdot}CO_2Et} CH(CO_2Et)_2{\cdot}CHMe{\cdot}[CH_2]_5{\cdot}CO_2Et$$
(XII.)

The only noteworthy step in these reactions is the preparation of ω-bromovaleric acid (XI) by a method analogous to that used for ω-bromoheptanoic acid (Ames, Bowman, and Mason, *J.*, 1950, 174); the yields were not so good but could probably be improved. Condensation of (X) and the sodio-tribenzyl derivative of (XII) appeared to proceed normally to give a keto-ester, which was submitted to catalytic debenzylation and subsequent decarboxylation in the usual manner. The product, however, was heterogeneous and was not obtained in sufficient yield for further investigation.

This example makes it evident that the difficulties likely to be associated with the preparation of branched-chain α-hydroxy-acids in a pure condition, and anomalies occurring at the later stages of the synthesis, render the acyloin method, as applied above, unsuitable for the synthesis of branched-chain unsaturated acids. On the other hand, the alkoxy-ketone route is particularly convenient for the synthesis of these acids in a high state of purity on account of the ease of preparation of the starting materials and of the ease of the subsequent stages of the synthesis.

$CH_3{\cdot}O{\cdot}[CH_2]_6{\cdot}CH(CO_2Et)_2$
(XIV.)

$CH_3{\cdot}[CH_2]_7{\cdot}CH(OMe){\cdot}CO{\cdot}[CH_2]_4{\cdot}OMe$
(XV.)

$CH_3{\cdot}[CH_2]_7{\cdot}CH(OMe){\cdot}CMe(OH){\cdot}[CH_2]_6{\cdot}OMe$ (XVI.)

Finally, we record some preliminary experiments on the synthesis of unsaturated acids bearing an alkyl substituent on the double bond. Subjection of 2-methoxydecanoyl chloride and ω-methoxyamylmalonic ester (XIV) to the debenzylation ketone synthesis furnished, in satisfactory yield, 7-keto-1 : 8-dimethoxyhexadecane (XV), which was converted by reaction with methylmagnesium iodide into the tertiary alcohol (XVI). Conversion of this into the corresponding tribromide proved difficult. Reaction with hydrogen bromide–acetic acid at 100° gave a dibromide in which, presumably, the terminal methoxy-group remained intact, but the presence of sulphuric acid brought about extensive decomposition. Rather surprisingly, however, the dibromide itself was sufficiently stable to sulphuric acid to permit further reaction

with hydrogen bromide to be carried out in its presence. The resulting crude tribromide (XVII) was then treated as follows:

$$CH_3\cdot[CH_2]_7\cdot CHBr\cdot CMeBr\cdot[CH_2]_6\cdot Br \xrightarrow{Zn} CH_3\cdot[CH_2]_7\cdot CH{:}CMe\cdot[CH_2]_6\cdot Br$$
(XVII.)

$$\xrightarrow{\text{Malonation; hydrolysis; decarboxylation.}} CH_3\cdot[CH_2]_7\cdot CH{:}CMe\cdot[CH_2]_7\cdot CO_2H \quad \text{(XVIII.)}$$

Although the resulting 9-methyloctadec-9-enoic acid (XVIII) and its precursors had unsatisfactory analyses, the acid itself had a fairly satisfactory iodine value (89; theory, 86) and on hydrogenation furnished the known 9-methyloctadecanoic acid.

Experimental.

The following general techniques have been used throughout this work and are collected here for present and future reference.

Esterifications.—(1) *Methyl esters.* The procedure is similar to that used by Brown *et al.* (*J. Org. Chem.*, 1947, **12**, 163) in which a mixture of the acid (0·25 mol.), chloroform (130 ml.), methanol (100 ml.), and sulphuric acid (1 ml.) is refluxed in an apparatus fitted with a Soxhlet thimble containing anhydrous magnesium or copper sulphate for 12 hours. The cooled solution is then washed successively with water, sodium hydrogen carbonate solution, and water, dried ($MgSO_4$), and distilled. The yield exceeded 90%.

(2) *Ethyl esters.* A mixture of the acid (1 mol.), benzene (500 ml.), ethanol (250 ml.), and sulphuric acid (1 ml.) is refluxed through a Fenske column (35 mm. of packing) fitted with a Dean and Stark separator, until no further phase separation takes place. The product is then worked up as in the previous example; the yield was >95%. For small quantities of acid (0·01 mol.) the phase separator is replaced by a reflux-head of the Whitmore–Lux pattern, and very slow distillation, under a high reflux-ratio, is allowed to take place until the temperature of the vapours rises to 68°.

Ketone Syntheses.—The method is that described in the preceding paper and elsewhere.

Reduction of Ketones.—The following procedure is, in our experience, far superior to any other catalytic method. The ester (0·05 mol.) is added to pre-reduced Raney nickel W7 (*ca.* 5 g.) (Adkins and Billica, *J. Amer. Chem. Soc.*, 1948, **70**, 698) in ethanol (250 ml.) in an atmosphere of hydrogen, and stirring is continued at room temperature (or up to 40°) until absorption of gas ceases. The catalyst is then filtered off and most of the solvent removed by distillation *in vacuo*. The residue is dissolved in light petroleum (b. p. 40—60°) and after being washed with water, dilute sulphuric acid, sodium hydrogen carbonate solution, and water, is distilled in the usual manner; the yield was ~95%.

Preparation of αβ-Dibromides.—The dihydroxy- or hydroxymethoxy-acid (1 vol.) is mixed with acetic acid containing dry hydrogen bromide (25%, *d* 1·2) (10 vols.), and sulphuric acid (2·5 vols.) added. After 8 hours at room temperature, the mixture is heated to 100° during 1 hour and kept at that temperature for a further 4 hours, whereafter more hydrogen bromide reagent (1 vol.) is added, and the mixture kept at 100° for 4 hours, cooled, poured into water, and extracted with benzene. The organic extract is then subjected to azeotropic esterification with ethanol, and the crude undistilled ester, dissolved in light petroleum (b. p. 40—60°; 200 ml. per 10 g.), is passed slowly through a column of activated alumina (15 cm. × 1·5 cm.). After being washed with the same solvent (400 ml.), the combined eluates are distilled; the yield exceeds 70%.

Unsaturated Acids.—Zinc dust (1 g.) in ethanol (5 ml.) containing hydrobromic acid (0·1 ml. of 50%) is boiled in an atmosphere of nitrogen for 5 minutes, and the dibromide (0·6 g.) added. After the ensuing exothermic reaction is complete, the solution is refluxed for 1 hour, and the zinc is filtered off and washed with light petroleum (b. p. 40—60°). The combined filtrates are then diluted with water, and the unsaturated ester isolated as usual and distilled (nitrogen leak). Hydrolysis of the ester is effected by refluxing it with excess of ethanolic sodium hydroxide ((N.) in an atmosphere of nitrogen. Ethanol is then removed by steam-distillation, and the unsaturated acid liberated by addition of dilute mineral acid and isolated in the usual manner.

4-Methyldecanoic Acid.—Following exactly the procedures used by Cason *et al.* (*loc. cit.*), the Grignard reagent from *n*-hexyl bromide (145 g.) and magnesium (21·5 g.) was allowed to react with ethyl lævulate (117 g.) in benzene, and the crude lactone (b. p. 140—150°/7 mm.) thus obtained was converted through the chloro-ethyl ester into the unsaturated ester. The latter (b. p. 103—108°/2 mm.; 62 g.) was dissolved in ethanol (150 ml.) and hydrogenated in the presence of palladised strontium carbonate (5 g. of 7%) and platinum oxide (0·7 g.) until absorption ceased (1 mol.). Hydrolysis of the product and isolation with benzene yielded 4-methyldecanoic acid as a colourless oil, b. p. 153—155°/10 mm. (49 g., 33% yield overall). The *p*-bromophenacyl ester separated from ethanol in needles, m. p. 43° (Polgar and Robinson, *J.*, 1945, 389, give m. p. 42°).

Methyl 2-Bromo-4-methyldecanoate.—The foregoing acid (48 g.) was converted into the chloride with thionyl chloride (60 ml.) and brominated (45 g. of bromine) by Papa and Schwenk's procedure (*loc. cit.*). After removal of excess of thionyl halides *in vacuo*, the product was gradually added to methanol (150 ml.), and the mixture set aside at room temperature for 48 hours. Addition of water, followed by extraction with chloroform and distillation through a Vigreux column, furnished the *methyl* ester as a pale yellow oil, b. p. 89°/0·1 mm. (62 g., 84%) (Found: C, 51·1; H, 8·4. $C_{12}H_{23}O_2Br$ requires C, 51·6; H, 8·3%).

2-*Methoxy*-4-*methyldecanoic Acid* (I).—Sodium (8·0 g.) was dissolved in dry methanol (150 ml.) and the foregoing ester (58 g.) was then added. After refluxing for 1 hour (bath, 110°) methanol (70 ml.) was distilled off, the residue poured into dilute sulphuric acid, and the product isolated with benzene. The crude product was then fractionated through a Fenske column fitted with a reflux-head, the separations being followed by refractive-index observations. A fore-run (5 g.) was rejected, and then *methyl* 2-*methoxy*-4-*methyldecanoate* (b. p. 91°/0·7 mm., n_D^{20} 1·4340; 30 g., 62%) was collected (Found : C, 67·6; H, 10·7. $C_{13}H_{26}O_3$ requires C, 67·8; H, 11·4%). It (30 g.) was hydrolysed with methanolic sodium hydroxide in the usual manner to give the *acid*, which distilled as a colourless oil, b. p. 112°/0·2 mm., n_D^{20} 1·4458 (Found : C, 66·9; H, 10·7. $C_{12}H_{24}O_3$ requires C, 66·6; H, 11·2%).

Ethyl 9-*Keto*-10-*methoxy*-12-*methyloctadecanoate* (II).—Thionyl chloride (25 ml.) was added to the foregoing acid (21 g.), and the whole was warmed at 30° for 2 hours and then at 60° for 1·5 hours; the excess of thionyl chloride was removed *in vacuo*, and 2-*methoxy*-4-*methyldecanoyl chloride* distilled as a colourless oil, b. p. 80/0·2 mm. (21 g.) (Found : Cl, 15·4. $C_{12}H_{23}O_2Cl$ requires Cl, 15·1%). This acid chloride (20 g.; 0·085 mol.) was condensed with tribenzyl sodioheptane-1 : 1 : 7-tricarboxylate (0·13 mol.) [from sodium (3·0 g.), the triethyl ester (41 g.), and benzyl alcohol (52 g.)]. The condensation products were isolated, debenzylated, and decarboxylated in the usual manner. Light petroleum (250 ml.; b. p. 40—60°) was added, and heptane-1 : 1 : 7-tricarboxylic acid removed by washing with aqueous ethanol (3 × 30 ml., 1 : 1 v/v) and then water (30 ml.). After drying ($MgSO_4$) and evaporation, the crude residue was esterified azeotropically. Distillation yielded crude methoxy-ester and then *ethyl* 9-*keto*-10-*methoxy*-12-*methyloctadecanoate* as a pale yellow oil, b. p. 184°/0·3 mm., n_D^{20} 1·4523 (14 g., 45%) (Found : C, 72·2; H, 11·5. $C_{22}H_{42}O_4$ requires C, 71·3; H, 11·4%).

12-*Methyloctadec*-9-*enoic Acid*.—The latter ester was reduced catalytically to give *ethyl* 9-*hydroxy*-10-*methoxy*-12-*methyloctadecanoate* as a colourless oil, b. p. 180°/0·15 mm., n_D^{20} 1·4549 (Found : C, 70·8; H, 11·6. $C_{22}H_{44}O_4$ requires C, 70·9; H, 11·9%), and by the general procedures this afforded *ethyl* 9 : 10-*dibromo*-12-*methyloctadecanoate*, a pale yellow oil, b. p. 212°/0·4 mm., n_D^{20} 1·4866 (Found : C, 52·3; H, 7·9; Br, 33·2. $C_{21}H_{40}O_2Br_2$ requires C, 52·1; H, 8·3; Br, 33·0%), *ethyl* 12-*methyloctadec*-9-*enoate*, a colourless oil, b. p. 154°/0·3 mm., n_D^{20} 1·4532 (Found : C, 77·4; H, 12·2%; I.V., 77·7. $C_{21}H_{40}O_2$ requires C, 77·7; H, 12·4%; I.V., 78·2), and finally, 12-*methyloctadec*-9-*enoic acid*, a colourless oil, b. p. 176°/0·4 mm., n_D^{20} 1·4620 (Found : C, 77·2; H, 12·0%; I.V., 85·0. $C_{19}H_{36}O_2$ requires C, 76·8; H, 12·2%; I.V., 85·6).

(−)-1-*Bromo*-3 : 7-*dimethyloctane*.—Purified (+)-citronellol (n_D^{20} 1·4569, $[\alpha]_D^{15}$ +3·60°) was hydrogenated by means of Adams's catalyst in the usual manner in ethanolic solution at atmospheric pressure, and the product converted into the bromide by use of hydrobromic–sulphuric acids followed by steam-distillation (Kamm and Marvel, *Org. Synth.*, 1921, **1**, 7). The product, (−)-1-bromo-3 : 7-dimethyloctane, was a colourless oil, b. p. 84°/6 mm., n_D^{20} 1·4554; $[\alpha]_D^{22}$ −4·97° (pure liquid).

(−)-2-*Ethoxy*-5 : 9-*dimethyldecanoic Acid*.—To a solution of potassium *tert.*-butoxide (0·35 mol.) in *tert.*-butanol (from 13·5 g. of metal and 250 ml. of the alcohol) were added ethyl ethoxymalonate (71·5 g., 0·35 mol.) and then the foregoing bromide (78 g., 0·35 mol.). After 12 hours' stirring under reflux (bath, 110°), dilute sulphuric acid was added to the cooled mixture, and the products were isolated with benzene and distilled.

(−)-*Ethyl ethoxy*-4 : 8-*dimethylnonane*-1 : 1-*dicarboxylate* was thus obtained as a colourless oil, b. p. 133—134°/0·5 mm., n_D^{20} 1·4386, $[\alpha]_D^{22}$ −2·11° (pure liquid) (92 g., 78%) (Found : C, 66·4; H, 11·0. $C_{19}H_{36}O_5$ requires C, 66·2; H, 10·5%). This ester (84 g.) with sodium hydroxide solution yielded the crude dicarboxylic acid, which was isolated with ethyl acetate–benzene (1 : 1) and decarboxylated by being heated at 180—190° (bath) till gas evolution ceased (30 mins.). To ensure complete conversion, the product was then resubmitted to the same procedures. Distillation then furnished (−)-2-*ethoxy*-5 : 9-*dimethyldecanoic acid* as a colourless, viscous oil, b. p. 136°/0·7 mm., n_D^{20} 1·4426, $[\alpha]_D^{20}$ −0·17° (54 g., 85%) (Found : C, 68·9; H, 11·8%; equiv., 243. $C_{14}H_{28}O_3$ requires C, 68·8; H, 11·5%; equiv., 244).

Triethyl 2 : 4-*Dimethylheptane*-1 : 1 : 7-*tricarboxylate* (VI).—Ethyl 7-keto-5-methyloctanoate (62 g.; Ames and Bowman, *loc. cit.*) was heated with ethyl cyanoacetate (32 g.), acetic acid (3 g.), ammonium acetate (2 g.), and benzene (35 ml.) according to Cope's method (*loc. cit.*) until no further water was collected. The cooled mixture was washed with water and distilled to give unchanged keto-ester (b. p. 80—90°/0·3 mm.; 25 g.) and the crude cyano-diester (b. p. 150—155°/0·4 mm.; 61 g.); the former fraction was then submitted to the same process again (total yield : 79 g., 87%). Hydrogenation of the product (79 g.) in ethanol (150 ml.) at 40—50° by aid of palladised strontium carbonate (3 g. of 10% Pd) proceeded readily and ceased when 1·05 mols. of hydrogen had been taken up. The filtered solution was concentrated *in vacuo* (130 ml.) and saturated with hydrogen chloride at 0°. After being kept at room temperature for 12 days, the mixture was gradually added to water (500 ml.) stirred with benzene (200 ml.); the separated benzene solution was evaporated under reduced pressure, and ethanol (200 ml.) and sulphuric acid (50 ml., 98%) were added to the residue. The solution was then refluxed for 8 hours and cooled, and the products were isolated as previously. The *triethyl* ester was obtained as a colourless, somewhat viscous oil, b. p. 144—145°/0·1 mm., n_D^{20} 1·4453 (70 g., 77%) (Found : C, 63·2; H, 9·5. $C_{19}H_{32}O_6$ requires C, 62·8; H, 9·4%).

Ethyl 10-*Ethoxy*-9-*keto*-5 : 7 : 13 : 17-*tetramethyloctadecanoate*.—A mixture of 2-ethoxy-5 : 9-dimethyldecanoic acid (50 g.) and thionyl chloride (50 ml.) was treated exactly as before to give the *chloride* as a colourless mobile oil, b. p. 120°/1 mm. (48 g.) (Found : Cl, 14·0. $C_{14}H_{27}O_3Cl$ requires Cl, 13·5%). This (36 g.) was added to a solution of tribenzyl sodio-2 : 4-dimethylheptane-1 : 1 : 7-tricarboxylate prepared from the triethyl ester (65 g.), benzyl alcohol (61 g.), and sodium (4·3 g.). The procedures then followed exactly those of the previous example, eventually yielding the *ethoxy-keto*-ester as an almost colourless oil, b. p. 190°/0·1 mm., n_D^{20} 1·4520 (17 g., 29%) (Found : C, 72·7; H, 11·8. $C_{26}H_{50}O_4$ requires C, 73·2; H, 11·8%).

5 : 7 : 13 : 17-*Tetramethyloctadec-9-enoic Acid.*—Reduction of the above ester furnished *ethyl* 10-*ethoxy*-9-*hydroxy*-5 : 7 : 13 : 17-*tetramethyloctadecanoate*, a colourless oil, b. p. 198—202°/0·5 mm., n_D^{20} 1·4550 (Found : C, 73·0; H, 12·0. $C_{34}H_{68}O_4$ requires C, 72·8; H, 12·2%), converted according to the general procedure into the corresponding dibromide. A portion of the latter was distilled, yielding a yellow oil, b. p. 225—230°/0·3 mm., n_D^{20} 1·4847 (slight decomposition occurred during the distillation) (Found : C, 54·4; H, 8·3; Br, 30·8. $C_{34}H_{66}O_3Br_2$ requires C, 54·7; H, 8·7; Br, 30·4%). The remainder was debrominated in the usual manner, furnishing *ethyl* 5 : 7 : 13 : 17-*tetramethyloctadec-9-enoate* as a colourless oil, b. p. 185°/0·5 mm., n_D^{20} 1·4555 (Found : C, 78·8; H, 12·6%; I.V., 69·0. $C_{34}H_{66}O_2$ requires C, 78·6; H, 12·7%; I.V., 69·2), converted by hydrolysis into the *acid*, a colourless oil, b. p. 185°/0·2 mm., n_D^{20} 1·4638 (Found : C, 78·4; H, 12·5%; I.V., 75·5. $C_{32}H_{64}O_2$ requires C, 78·0; H, 12·5%; I.V., 74·9). A sample of this acid (0·6 g.) in ethyl acetate (40 ml.) was shaken in hydrogen in the presence of palladised strontium carbonate for 2 hours. The filtered solution was then distilled, giving 5 : 7 : 13 : 17-*tetramethyloctadecanoic acid*, a colourless, somewhat viscous oil, b. p. 180°/0·1 mm., n_D^{20} 1·4566 (Found : C, 77·4; H, 12·8. $C_{32}H_{64}O_2$ requires C, 77·6; H, 13·0%).

3-*Methyldecanoic Acid.*—Nonan-2-one (b. p. 84°/20 mm.; 110 g.) was condensed with ethyl cyanoacetate by Cope's method (*loc. cit.*), and the crude product (b. p. 120—130°/0·5 mm.; 136 g.) hydrogenated in ethanol (200 ml.) in the presence of palladised strontium carbonate until absorption ceased (1·08 mols.). The filtered solution was evaporated under reduced pressure, and the residue hydrolysed by boiling for 25 hours with potassium hydroxide (130 g.), water (150 ml.), and ethylene glycol (100 ml.). After acidification with excess of dilute sulphuric acid, the product was extracted with benzene–ethyl acetate (1 : 1), and the solution washed with water, dried (Na_2SO_4), and evaporated. The residue was heated (bath, 180—190°) until decarboxylation ceased, and then distilled, yielding 3-methyldecanoic acid as a colourless oil, b. p. 125°/0·3 mm., n_D^{20} 1·4411 (87 g., 60%).

Ethyl 2-*Hydroxy*-3-*methyldecanoate.*—The foregoing acid was converted in exactly the same manner as used for the 4-isomer into *ethyl* 2-*bromo*-3-*methyldecanoate*, a colourless oil, b. p. 110°/0·5 mm., n_D^{20} 1·4592 (98% yield) (Found : C, 54·0; H, 9·0. $C_{13}H_{25}O_3Br$ requires C, 53·2; H, 8·6%). The latter (135 g.) was added in portions to a solution of potassium acetate (128 g.) in glacial acetic acid, and the mixture refluxed for 10 hours. Acetic acid was removed by distillation under reduced pressure, and water (500 ml.) added, the product being extracted with benzene. After removal of solvent, the residue was hydrolysed with boiling ethanolic sodium hydroxide, and ethanol distilled off in steam. The cooled solution was acidified with excess of dilute acid, and the product extracted with benzene–ethyl acetate (1 : 1); the extracts were washed three times with water, dried (Na_2SO_4), and evaporated *in vacuo*. The viscous, oily residue could not be induced to crystallise and was therefore esterified azeotropically, and the ester fractionated through a short Fenske column. After low-boiling products (7 g.) had been removed, the *hydroxy*-ester was collected as a colourless oil, b. p. 100—101°/0·5 mm., n_D^{20} 1·4405 (57 g., 54%) (Found : C, 68·1; H, 11·3. $C_{13}H_{26}O_3$ requires C, 67·8; H, 11·4%).

2-*Acetoxy*-3-*methyldecanoic Acid.*—Hydrolysis of the foregoing ester in the usual manner afforded the oily hydroxy-acid, which was treated with acetyl chloride (75 ml.) in portions, and the mixture set aside at room temperature for 15 hours. Distillation under reduced pressure yielded the *acid* as an almost colourless, viscous oil, b. p. 148°/0·2 mm., n_D^{20} 1·4451 (30 g., 50%) (Found : C, 64·5; H, 10·0%; equiv., 243. $C_{15}H_{28}O_4$ requires C, 63·9; H, 10·0%; equiv., 244).

2-*Acetoxy*-3-*methyldecanoyl Chloride.*—The preceding acid (25 g.) was warmed with thionyl chloride (30 ml.) at 35° for 2 hours and then at 45° for 1 hour. Distillation of the mixture under reduced pressure yielded the *chloride* as a colourless oil, b. p. 95°/0·2 mm. (22 g.) (Found : Cl, 13·8. $C_{15}H_{25}O_3Cl$ requires Cl, 13·5%).

5-*Bromopentanoic Acid.*—3-Chloropropanol (Gough and King, *J.*, 1928, 2439) was treated with sodiomalonic ester in the manner used for 7-bromoheptanoic acid (Ames, Bowman, and Mason, *loc. cit.*) to give 5-bromopentanoic acid (f. p. 36°; 21%).

Ethyl 7-*Keto-octanoate.*—The foregoing acid (70 g.) was esterified azeotropically, and the crude, undistilled ester treated with ethyl sodioacetoacetate (0·75 mol.) in dioxan (200 ml.) for 8 hours under reflux, the products being isolated in the usual manner. The crude residue was then boiled with glacial acetic acid (120 ml.) and concentrated sulphuric acid (1·5 g.) for 6 hours; sodium acetate (3·4 g.) was added, and after removal of acetic acid *in vacuo*, the residue was subjected to azeotropic esterification to give ethyl 7-keto-octanoate as a colourless oil, b. p. 113—115°/2 mm. (39 g., 54%).

Triethyl 6-*Methylheptane*-1 : 1 : 7-*tricarboxylate.*—A mixture of the aforementioned ester (39 g.), ethyl cyanoacetate (20 g.), ammonium acetate (1·5 g.), glacial acetic acid (2·0 g.), and benzene (25 ml.) was refluxed in a flask fitted with a Dean and Stark separator until no more water separated (Cope *et al.*, *loc. cit.*). The solution was washed with water, dried, and distilled to give the crude cyano-diester (37 g.; b. p. 160—170°/0·5 mm.) which was hydrogenated as previously. The crude product was then dissolved in ethanol–benzene (40 ml. each) and the solution saturated with dry hydrogen chloride at 0°; the mixture was kept at room temperature for 10 days and poured into water (250 ml.). The product was isolated with benzene and distilled to give the *triethyl* ester as a colourless, somewhat viscous oil, b. p. 157—159°/0·2 mm., n_D^{20} 1·4460 (33 g., 47%) (Found : C, 62·1; H, 9·2. $C_{17}H_{30}O_6$ requires C, 61·8; H, 9·2%).

Attempted Synthesis of Ethyl 10-*Hydroxy*-9-*keto*-7 : 11-*dimethyloctadecanoate.*—The foregoing triethyl ester (27·5 g.) was converted by reaction with sodium (1·9 g.) and benzyl alcohol (27 g.) in the usual manner into the corresponding tribenzyl ester, which was condensed with 2-acetoxy-3-methyldecanoyl chloride (21 g.). The product was isolated, debenzylated, and decarboxylated by the general procedure and then esterified azeotropically with methanol. Isolated in the usual manner, the ester was distilled under reduced pressure, but persistent decomposition occurred and a considerable residue which could not be distilled was obtained. The total distillate was redistilled and furnished a fraction of wide boiling range (160—210°/0·1 mm.; 8 g.) which could not be purified.

Diethyl 6-*Methoxyhexane*-1 : 1-*dicarboxylate*.—5-Bromo-1-methoxypentane (b. p. 81—82°/30 mm., n_D^{20} 1·4550) was prepared the method of Drake *et al.* (*J. Amer. Chem. Soc.*, 1946, **68**, 1537) and purified by fractional distillation through a Fenske column. The product (70 g.) was added to a solution of ethyl sodiomalonate (0·38 mol.) in ethanol (250 ml.), and the mixture refluxed for 1·5 hours and then poured into water. After isolation in the usual manner, the product was fractionated through a Fenske column fitted with a reflux-head, furnishing the *diethyl* ester as a colourless oil, b. p. 117—118°/0·7 mm., n_D^{20} 1·4346 (63 g., 63%) (Found : C, 60·2; H, 9·4. $C_{13}H_{24}O_5$ requires C, 60·0; H, 9·4%).

7-*Keto*-1 : 8-*dimethoxyhexadecane*.—The dibenzyl sodio-ester prepared from the foregoing ethyl ester (63 g.), sodium (5·5 g.), and benzyl alcohol (52 g.) was condensed with 2-methoxydecanoyl chloride (51 g.), and the product isolated, debenzylated, and decarboxylated by the general procedures. The resulting oil was shaken with light petroleum (b. p. 80—100°; 50 ml.) and water (200 ml.), and the mixture basified to phenolphthalein with sodium hydroxide (2N.) and heated to 50°; the aqueous layer was separated and extracted with fresh solvent, and the combined organic extracts were washed with water, dried, and distilled to give the *ketone* as a colourless oil, b. p. 138—140°/0·1 mm., n_D^{20} 1·4472 (47 g., 68%) (Found : C, 71·7; H, 11·9. $C_{18}H_{36}O_3$ requires C, 72·0; H, 12·0%).

7-*Hydroxy*-1 : 8-*dimethoxy*-7-*methylhexadecane*.—The foregoing ketone (15 g.) was added during 10 minutes to the Grignard reagent prepared from magnesium (2·4 g.) and methyl iodide (14 g.) in ether (50 ml.), the mixture being stirred at 0° during the addition and for a further 10 minutes and then refluxed for 30 minutes. The reaction mixture was cooled to 0° and decomposed with ammonium chloride (25 g.) in water (50 ml.) containing ice, the product being taken up in light petroleum (b. p. 40—60°). After being washed with water and dried (K_2CO_3), the solution was distilled, giving 7-*hydroxy*-1 : 8-*dimethoxy*-7-*methylhexadecane* as a colourless, slightly viscous oil, b. p. 157—158°/0·4 mm., n_D^{20} 1·4520 (14 g., 88%) (Found : C, 72·3; H, 12·6. $C_{19}H_{40}O_3$ requires C, 72·1; H, 12·7%).

Attempts to prepare 1 : 7 : 8-*Tribromo*-7-*methylhexadecane*.—(*a*) The foregoing alcohol (8 g.) was dissolved in hydrogen bromide–acetic acid (*d* 1·25, 80 ml.) at room temperature, and after 1 hour, concentrated sulphuric acid (20 ml.) was added in portions with cooling and shaking. After 20 hours, the mixture was reddish-orange and an oily layer has settled out; the mass was heated to 100° during 1 hour, kept at that temperature for 7 hours, and poured into water. The product was a black resinous material which was not examined further.

(*b*) Hydrogen bromide in acetic acid (*d* 1·25; 50 ml.) was mixed with the *tert.*-alcohol (15 g.) at room temperature, and after 60 hours the mixture was heated at 100° for 10 hours. After addition of water, the products were taken up in light petroleum (b. p. 40—60°; 400 ml.), and the solution was decolorised by passage through a 40-cm. column of kieselguhr–activated charcoal, the same solvent (500 ml.) being used for elution. Evaporation of the total eluates yielded crude 7 : 8-*dibromo*-1-*methoxy*-7-*methylhexadecane*, a pale yellow oil, n_D^{20} 1·4944 (16 g.) (Found : Br, 39·4. $C_{18}H_{36}O_2Br_2$ requires Br, 37·4%).

(*c*) This product (15 g.) was treated with hydrogen bromide–acetic acid–sulphuric acid as in (*a*) to give a dark red oil (18 g.; n_D^{20} 1·5265) which was probably crude 1 : 7 : 8-tribromo-7-methylhexadecane (Found : Br, 56·4. Calc. for $C_{17}H_{33}Br_3$: Br, 50·3%).

1-*Bromo*-7-*methylhexadec*-7-*ene*.—Debromination of the crude tribromide (18 g.) by activated zinc in the usual manner furnished a dark red oil, which was distilled, giving impure bromo-olefin as a yellow oil, b. p. 140—170°/0·2 mm., n_D^{20} 1·4875 (6·5 g.) (Found : Br, 28·0. Calc. for $C_{17}H_{33}Br$: Br, 25·2%).

9-*Methyloctadec*-9-*enoic Acid*.—The foregoing bromide was treated with excess of sodiomalonic ester (4 mols.) in ethanol in the usual manner to give *diethyl* 8-*methylheptadec*-8-*ene*-1 : 1-*dicarboxylate*, an almost colourless oil, b. p. 198—202°/0·5 mm., n_D^{20} 1·4613 (Found : C, 70·7; H, 10·2%; I.V., 62·2. $C_{24}H_{44}O_4$ requires C, 72·7; H, 11·2%; I.V., 64·0). This was hydrolysed in the usual manner, and the product isolated, decarboxylated at 190° and then distilled. 9-*Methyloctadec*-9-*enoic acid* was thus obtained as a colourless oil, b. p. 178—180°/0·4 mm., n_D^{20} 1·4710 (Found : C, 75·2; H, 11·4%; I.V., 87·9. $C_{19}H_{36}O_2$ requires C, 76·8; H, 12·2%; I.V., 85·6).

A portion of the unsaturated acid was hydrogenated in the same manner as for the tetramethyloleic acid, furnishing a crude product which solidified at room temperature and crystallised from acetone at −20°, yielding colourless plates of 9-methyloctadecanoic acid, m. p. 37·5—38·5° (Found : C, 75·9; H, 12·5. Calc. for $C_{19}H_{38}O_2$: C, 76·4; H, 12·8%). Cason and Winans (*J. Org. Chem.*, 1950, **15**, 139) recorded m. p. 38·5—39·1°.

The authors thank the Medical Research Council for a grant which enabled one of them (D. E. A.) to participate in this work.

BIRKBECK COLLEGE, LONDON, E.C.4. *Received, December 6th*, 1950.]

240. *Triterpene Resinols and Related Acids. Part XXI.* iso-α-*Amyrenonol-II.*

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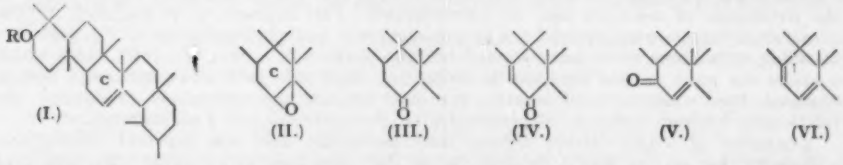
A study of the relation of the isomeric αβ-unsaturated ketones, α-amyrenonol and *iso*-α-amyrenonol, to α-amyradienol is described. Oxidation of α-amyradienyl acetate with perbenzoic acid gives a mixture from which α-amyrenonyl acetate and *iso*-α-amyrenonyl acetate have been isolated. Oxidation of the dienyl acetate with hydrogen peroxide on the other hand gives a mixture from which α-amyrenonyl acetate and an isomeric αβ-unsaturated ketone, *iso*-α-amyrenonyl-II acetate, have been isolated, and a similar mixture is obtained by oxidation of α-amyradienyl benzoate with hydrogen peroxide. *iso*-α-Amyrenonol-II is probably a stereoisomer of *iso*-α-amyrenonol, into which it can be converted by prolonged treatment with strong alkali. Reduction of *iso*-α-amyrenonyl-II esters with sodium and amyl alcohol followed by treatment of the reaction product with acetic anhydride gives α-amyradienyl acetate. These reactions establish the relations between the three αβ-unsaturated ketones and α-amyradienol. *iso*-α-Amyrenonol-II differs from *iso*-α-amyrenonol in that it can be catalytically reduced to give a saturated ketone, α-amyranonol-II. It is concluded that angular methyl group migration does not occur in the conversion of α-amyrin into *iso*-α-amyradienonol and that the reactions of the latter compound are yet to be satisfactorily interpreted.

OXIDATION of α-amyrin benzoate (I; * R = COPh) with hydrogen peroxide gives an oxide (II) which, when rearranged with mineral acid yields the saturated ketone, α-amyranonyl benzoate (III). Bromination of either the oxide or the ketone gives *iso*-α-amyrenonyl benzoate (cf. IV), and the related *iso*-α-amyrenonyl acetate is obtained by a similar series of changes from α-amyrin acetate (Seymour, Sharples, and Spring, *J.*, 1939, 1079; Seymour and Spring, *J.*, 1941, 319; Silverstone and Spring, *J.*, 1951, 935). Oxidation of α-amyrin acetate with chromic acid gives an isomeric αβ-unsaturated ketone, α-amyrenonyl acetate (V) (Spring and Vickerstaff, *J.*, 1937, 249), which has the same nuclear structure as α-amyrin (Ruzicka, Leuenberger, and Schellenberg, *Helv. Chim. Acta*, 1937, **20**, 1271). Reduction of the two αβ-unsaturated ketones,



(I.) (II.) (III.) (IV.) (V.) (VI.)

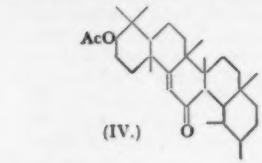
α-amyrenonyl acetate and *iso*-α-amyrenonyl acetate, with sodium and alcohol, followed by acetylation of the reaction products, gives in each case α-amyradienyl acetate (VI) (Spring and Vickerstaff, *loc. cit.*; Ewen, Spring, and Vickerstaff, *J.*, 1939, 1303; Seymour, Sharples, and Spring, *loc. cit.*); α-amyradienyl acetate can also be obtained by partial dehydrogenation of α-amyrin acetate with sulphur (Jacobs and Fleck, *J. Biol. Chem.*, 1930, **88**, 137) or with *N*-bromosuccinimide (Ruzicka, Jeger, and Redel, *Helv. Chim. Acta*, 1943, **26**, 1235).

The structure of *iso*-α-amyrenonol has assumed considerable importance in the chain of evidence upon which depends the recently postulated structure (I; R = H) for α-amyrin (Meisels, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1949, **32**, 1075) particularly in so far as its relation to β-amyrin is concerned. Oxidation of *iso*-α-amyrenonyl acetate (IV) with selenium dioxide gives *iso*-α-amyradienonyl acetate (Ruzicka, Rüegg, Volli, and Jeger, *Helv. Chim. Acta*, 1947, **30**, 140), and this reaction has been formulated as involving a molecular rearrangement in which a methyl group migrates from $C_{(14)}$ to $C_{(13)}$ (Meisels, Jeger, and Ruzicka, *Helv. Chim. Acta*, 1950, **33**, 700; Rüegg, Dreiding, Jeger, and Ruzicka, *ibid.*, p. 889), *iso*-α-amyradienonyl acetate being represented as (VII). *iso*-α-Amyradienonyl acetate has been

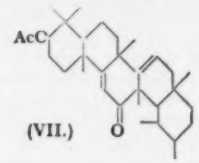
* For descriptive convenience the formula for α-amyrin advocated by Meisels, Jeger, and Ruzicka (*Helv. Chim. Acta*, 1949, **32**, 1075) is employed in this paper.

converted into a compound formulated as the β-diketone (VIII) by a series of reactions including oxidation at the $C_{(14)}$–$C_{(15)}$ ethylenic linkage followed by a pyrolytic decomposition. Although this β-diketone does not give a coloration with ferric chloride it reacts with diazomethane to give two isomeric compounds formulated as the methyl ethers (IX) and (X) which are identical with two products obtained by similar reactions starting from *iso*-β-amyrenonyl acetate.

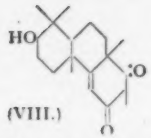
It is the purpose of this paper to examine the premises upon which the assumption of a methyl group migration, in the reactions leading to the formation of *iso*-α-amyradienonyl acetate, is made. In addition to its bearing upon the structure of *iso*-α-amyradienonyl acetate, a decision that methyl group migration has occurred during these reactions, which involve relatively mild reaction conditions, may have wider repercussions in a consideration of the mechanism of formation of the products of total dehydrogenation of the triterpenoids.



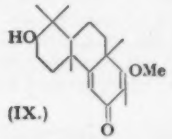
(IV.)



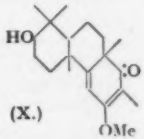
(VII.)



(VIII.)



(IX.)



(X.)

The formulæ (IV) and (VII) for *iso*-α-amyrenonyl acetate and *iso*-α-amyradienonyl acetate, respectively, cannot both be correct since it is known that catalytic hydrogenation of *iso*-α-amyradienonyl acetate gives *iso*-α-amyrenonyl acetate in good yield (Ruzicka, Rüegg, Volli, and Jeger, *loc. cit.*). The possibility that a methyl group attached to $C_{(13)}$ in *iso*-α-amyradienonyl acetate again migrates to $C_{(14)}$ during the catalytic hydrogenation seems remote and in our opinion is excluded by the fact that *iso*-α-amyradienonyl acetate is recovered unchanged after being shaken in the absence of hydrogen in acetic acid with a freshly reduced platinum catalyst.* It follows that *iso*-α-amyrenonyl acetate and *iso*-α-amyradienonyl acetate have the same nuclear structure, and it becomes necessary to consider the possibility of methyl group migration during the conversion of α-amyrin into *iso*-α-amyrenonol. This appears to be excluded by the observation that *iso*-α-amyrenonol can be converted into α-amyradienyl acetate (VI), oxidation of which with ozone gives α-amyrenonyl acetate (Ewen and Spring, *J.*, 1940, 1196) which contains the same nuclear structure as α-amyrin. Since the yield of α-amyrenonyl acetate obtained from α-amyradienyl acetate was only 4%, it was decided to re-examine the relationship between α-amyrin, α-amyrenonol, *iso*-α-amyrenonol, and α-amyradienol.

Oxidation of α-amyradienyl acetate with perbenzoic acid was reported (Spring and Vickerstaff, *loc. cit.*) to give a product, m. p. 192°, described as an oxide. We find that chromatographic fractionation of the reaction mixture obtained by oxidation of α-amyradienyl acetate with perbenzoic acid gives *iso*-α-amyrenonyl acetate in 20% yield together with α-amyrenonyl acetate in approximately 7% yield; these are minimum yields, considerable losses occurring in the tedious purification procedure employed. Oxidation of α-amyradienyl benzoate with hydrogen peroxide gives a mixture from which α-amyrenonyl benzoate in approximately 16% yield has been isolated, together with a 42% yield of an isomeric compound which we name *iso*-α-amyrenonyl-II benzoate. The separation of this mixture was achieved by a process of fractional crystallisation from boiling ethanol which was developed after unsuccessful attempts to separate the mixture by chromatography. *iso*-α-Amyrenonyl-II benzoate was characterised by hydrolysis to *iso*-α-amyrenonol-II, acetylation of which yields *iso*-α-amyrenonyl-II acetate. The last compound is also obtained in approximately 7% yield by the oxidation of α-amyradienyl acetate with hydrogen peroxide, the major product of this reaction being an approximately 72% yield of α-amyrenonyl acetate. α-Amyrenonyl acetate and *iso*-α-amyrenonyl-II acetate form a constant-melting mixed crystal which cannot be separated by chromatography on alumina or by ordinary methods of crystallisation. The compound described as *epi*(*iso*)-α-amyrenonyl acetate obtained together with α-amyrenonyl

* This observation was made by Dr. Wm. Manson to whom we express our thanks.

acetate by the action of ozone on α-amyradienyl acetate (Ewen and Spring, *loc. cit.*) is probably a mixed crystal of α-amyrenonyl acetate and *iso*-α-amyrenonyl-II acetate. *iso*-α-Amyrenonyl-II acetate is an αβ-unsaturated ketone; it exhibits an absorption maximum at 2500 A. ($\varepsilon = 11{,}000$) and gives no coloration with tetranitromethane in chloroform. Reduction of *iso*-α-amyrenonyl-II acetate or benzoate with sodium and amyl alcohol followed by treatment of the product with acetic anhydride gave α-amyradienyl acetate. Prolonged treatment of *iso*-α-amyrenonyl-II benzoate with strong alkali converts it quantitatively into *iso*-α-amyrenonol thus establishing that *iso*-α-amyrenonol-II differs from *iso*-α-amyrenonol either in the position of the ethylenic linkage (which in both cases must be αβ with respect to the carbonyl group) or, more likely, in the orientation of the hydrogen atom attached to the α-carbon with respect to the carbonyl group. A significant difference is to be observed in the behaviour of *iso*-α-amyrenonol and *iso*-α-amyrenonol-II; in contrast to the former compound (cf. Jeger, Rüegg, and Ruzicka, *Helv. Chim. Acta*, 1947, **30**, 1294) *iso*-α-amyrenonol-II is smoothly reduced with hydrogen and platinum to a saturated ketone, α-amyranonol-II.

The formation, in high yield, of α-amyrenonyl acetate by the oxidation of α-amyradienyl acetate, and the inter-relation of *iso*-α-amyrenonyl acetate and α-amyrenonyl acetate through α-amyradienyl acetate lead to the conclusion that all these compounds have the same carbon skeleton and specifically that the conversion of α-amyrin into *iso*-α-amyrenonyl acetate does not involve the migration of an angular methyl group. Since *iso*-α-amyradienonyl acetate is smoothly converted into *iso*-α-amyrenonyl acetate (and α-amyradienyl acetate) by simple catalytic hydrogenation, the formation of *iso*-α-amyradienonyl acetate from α-amyrin has likewise not involved angular methyl group migration, and the presence of an angular methyl group at $C_{(14)}$ appears to be impossible. A satisfactory interpretation of the reactions of *iso*-α-amyradienonyl acetate leading to the formation of common degradation products of the α- and β-amyrins is yet to be given.

Experimental.

Specific rotations were measured in chloroform solution, a 1-dm. tube being used; m. p.s are uncorrected.

Oxidation of α-Amyradienyl Acetate with Perbenzoic Acid.—α-Amyradienyl acetate (1·6 g.) was treated with 0·6N-perbenzoic acid in chloroform (50 c.c.), and the solution kept at 2° for 14 days. The solution was washed with aqueous sodium carbonate and water, dried over sodium sulphate, and evaporated. The resin was dissolved in light petroleum (b. p. 40—60°) and filtered through a column of activated alumina (40 g.).

The column was washed with light petroleum (2000 c.c.) and then developed with benzene. The first 500 c.c. of this solvent eluted a crystalline solid (fraction *A*; 0·48 g.). The small quantity of material eluted by the next 750 c.c. was ignored, and a further 500 c.c. of benzene gave more crystalline solid (fraction *B*; 0·14 g.).

Fraction *A* was recrystallised from methanol–chloroform giving *iso*-α-amyrenonyl acetate (300 mg.), m. p. 282—283°, $[\alpha]_D^{18}$ +89° (*c*, 1·3), undepressed in m. p. when mixed with a specimen, m. p. 283—284°, $[\alpha]_D^{18}$ +87°, prepared as described by Seymour, Sharples, and Spring (*loc. cit.*).

Fraction *B* was similarly recrystallised from methanol–chloroform, yielding α-amyrenonyl acetate (90 mg.), m. p. 275—276°, $[\alpha]_D^{18}$ +96° (*c*, 0·7), undepressed when mixed with an authentic specimen, m. p. 276°, $[\alpha]_D^{18}$ +98° (*c*, 1·7), obtained by Spring and Vickerstaff's method (*loc. cit.*).

iso-α-*Amyrenonyl-II Benzoate.*—A solution of α-amyradienyl benzoate (5 g.) in glacial acetic acid (225 c.c.) was treated for 20 minutes at steam-bath temperature with a mixture of hydrogen peroxide (30%; 20 c.c.) and glacial acetic acid (20 c.c.) with vigorous stirring. Stirring and heating were continued until the precipitated solid redissolved (2 hours). More peroxide–acetic acid (40 c.c.) was added and the solution heated and stirred for 1 hour. The solution was diluted with hot water until it was permanently turbid. The crystalline solid (fraction I) separating on cooling was collected, washed with a little methanol and then with water, and dried in air at 100°. The mother-liquor was diluted with water, and the solid (fraction II) collected, washed with water, and dried in a vacuum.

Fraction I was dissolved in chloroform (3 c.c.) and ethanol (200 c.c.), and the solution evaporated until crystallisation occurred in the boiling mixture. The boiling mixture was filtered and the filtrate again concentrated until crystallisation occurred. Three crops of crystalline solid (mother-liquor *A*) obtained by this procedure were combined and recrystallised from chloroform–methanol giving iso-α-*amyrenonyl-II benzoate* (2·1 g.) as large needles, m. p. 242°, $[\alpha]_D^{18}$ +21° (*c*, 3·0) (Found: C, 81·5; H, 9·8. $C_{37}H_{52}O_3$ requires C, 81·6; H, 9·6%).

iso-α-*Amyrenonol-II.*—A solution of *iso*-α-amyrenonyl-II benzoate (250 mg.) in benzene (5 c.c.) was treated with a solution of potassium hydroxide (250 mg.) in water (2 c.c.) and ethanol (20 c.c.). The mixture was refluxed for 2 hours, cooled, and poured into ice-cold dilute sulphuric acid. The reaction product was isolated by means of ether and crystallised from chloroform–light petroleum (b. p. 60—80°) giving iso-α-*amyrenonol-II* (150 mg.) as long feathery needles, m. p. 211—212°, $[\alpha]_D$ −15·5° (*c*, 3·4) (Found: C, 81·9; H, 10·7. $C_{30}H_{48}O_3$ requires C, 81·8; H, 11·0%).

α-*Amyrenonyl Benzoate.*—Fraction II of the oxidation product from α-amyradienyl benzoate was combined with the mother-liquor *A* and crystallised. The first two crystalline fractions were combined

and recrystallised from chloroform–methanol giving α-amyrenonyl benzoate (800 mg.) as plates, m. p. 275—276°, $[\alpha]_D$ +107° (*c*, 4·4) (Found : C, 81·3; H, 8·55. Calc. for $C_{37}H_{52}O_3$: C, 81·6; H, 9·6%); the m. p. was undepressed when this material was mixed with a specimen, m. p. 274—275°, $[\alpha]_D$ +107° (*c*, 3·3), obtained as described by Spring and Vickerstaff (*loc. cit.*).

iso-α-*Amyrenonyl*-II *Acetate*.—(*a*) Acetylation of *iso*-α-amyrenonol-II with pyridine and acetic anhydride gave iso-α-*amyrenonyl*-II *acetate* from chloroform–methanol as needles, m. p. 200—201°, $[\alpha]_D^{16}$ +11° (*c*, 1·8). Light absorption in ethanol : Maximum at 2500 A. ; ε = 11,000.

(*b*) α-Amyradienyl acetate (5 g.) was oxidised with hydrogen peroxide. Following the conditions detailed for the corresponding benzoate a crystalline fraction and an amorphous fraction were obtained. The crystalline fraction separating from the aqueous acetic acid solution was fractionally crystallised at the boiling point of ethanol. The first four fractions were combined and recrystallised from chloroform–methanol giving α-amyrenonyl acetate (3·6 g.) as large plates, m. p. 276°, $[\alpha]_D^{16}$ +96° (*c*, 1·7) (Found : C, 79·9; H, 10·2. Calc. for $C_{32}H_{50}O_3$: C, 79·6; H, 10·4%). Light absorption in ethanol : Maximum at 2520 A. ; ε = 12,000. The m. p. was undepressed when the product was mixed with a specimen of α-amyrenonyl acetate prepared by Spring and Vickerstaff's method (*loc. cit.*).

The amorphous product obtained by dilution of the aqueous acetic acid mother-liquors with water was combined with the ethanol mother-liquors from the fractional crystallisation described above, and the solution concentrated to a small bulk. The crystalline solid separating was collected after four days and recrystallised from chloroform–methanol giving a solid (0·7 g.), m. p. 193°, which was fractionally crystallised from boiling methanol. The first fraction (0·11 g.) melted over a range above 220°. The second and third fractions were combined and recrystallised from chloroform–methanol giving *iso*-α-amyrenonyl-II acetate (0·35 g.) as needles, m. p. 200—202° undepressed when mixed with the specimen obtained by method (*a*), $[\alpha]_D^{18}$ +14° (*c*, 0·9) (Found : C, 79·3; H, 10·8. $C_{32}H_{50}O_3$ requires C, 79·6; H, 10·4%).

Hydrolysis of the acetate obtained by method (*b*) using the method described for the benzoate gave *iso*-α-amyrenonol-II, which separated as long feathery needles from chloroform–light petroleum (b. p. 60—80°), m. p. 211—213° undepressed when mixed with the specimen described above, $[\alpha]_D^{16}$ −16 (*c*, 1·8). Light absorption in ethanol : Maximum at 2500 A., ε = 12,000.

α-*Amyradienyl Acetate*.—A boiling solution of *iso*-α-amyrenonyl-II benzoate (3 g.) in dry amyl alcohol (120 c.c.) was treated with sodium (7·5 g.) added during 20 minutes. Amyl alcohol (20 c.c.) was added and the mixture refluxed for 40 minutes. After being washed with water, the amyl alcohol was removed in steam, the reaction mixture extracted with ether, and the extract dried (Na_2SO_4). The product obtained by removal of the ether was heated under reflux for 1 hour with acetic anhydride (20 c.c.), and the mixture was then diluted with water and kept overnight. The precipitated solid was collected and crystallised from chloroform–methanol giving α-amyradienyl acetate (1·6 g.), as needles, m. p. 168°, $[\alpha]_D^{16}$ +313° (*c*, 1·6) (Found : C, 81·9; H, 10·5. Calc. for $C_{32}H_{50}O_3$: C, 82·3; H, 10·8%).

Similar reduction of *iso*-α-amyrenonyl-II acetate (300 mg.) gave α-amyradienyl acetate (200 mg.), m. p. 166° undepressed when the material was mixed with the specimen described above. Light absorption in ethanol : Maximum at 2830 A., ε = 9000. A specimen of α-amyradienyl acetate, obtained by reduction of α-amyrenonyl benzoate with sodium and amyl alcohol followed by acetylation, separated from chloroform–methanol as needles, m. p. 168—169°, $[\alpha]_D^{16}$ +318° (*c*, 1·2).

iso-α-*Amyrenonol*.—*iso*-α-Amyrenonyl-II benzoate (3 g.) in ethanol (140 c.c.) was mixed with potassium hydroxide (11 g.) in water (10 c.c.) and ethanol (20 c.c.), and the solution refluxed for 6 hours. After the addition of potassium hydroxide (7 g.) in water (5 c.c.) and ethanol (20 c.c.) refluxing was continued for 8 hours. The mixture was poured into water (1 l.) and extracted with ether. The washed and dried extract was evaporated and the product crystallised from methanol and from chloroform–light petroleum (b. p. 100—120°) giving *iso*-α-amyrenonol (2·1 g.), m. p. 239°, $[\alpha]_D^{18}$ +75° (*c*, 2·1), undepressed in m. p. when mixed with an authentic specimen. Acetylation gave *iso*-α-amyrenonyl acetate, m. p. 285°, $[\alpha]_D^{16}$ +84°, identical with a specimen, m. p. 283—284°, $[\alpha]_D$ +87° (*c*, 2·1), prepared as described by Seymour, Sharples, and Spring (*loc. cit.*).

α-*Amyranonol*-II.—A solution of *iso*-α-amyrenonol-II (0·6 g.) in glacial acetic acid (150 c.c.) was shaken with hydrogen in the presence of platinum (from 0·2 g. of platinum oxide) at room temperature. Absorption of hydrogen was rapid and ceased after one hour; it then corresponded to 1·1 mols. After 6 hours the mixture was filtered and the acetic acid removed under reduced pressure at 40°. The crystalline residue was recrystallised from chloroform–methanol giving α-amyranonol-II (530 mg.) as large hexagonal plates, m. p. 258—260° (sintering at 244°), $[\alpha]_D^{18}$ +58·5° (*c*, 2·0) (Found : C, 81·9; H, 11·6. $C_{30}H_{50}O_2$ requires C, 81·4; H, 11·4%).

α-*Amyranonyl*-II *Acetate*.—(*a*) *iso*-α-Amyrenonyl-II acetate (300 mg.) in glacial acetic acid (250 c.c.) was shaken with hydrogen in the presence of platinum (from 200 mg. of platinum oxide) at 20° for 16 hours; the hydrogen absorption then approximated to 1·2 mols. The product was crystallised from chloroform–ethanol giving α-*amyranonyl*-II *acetate* (280 mg.) as needles, m. p. 216°, $[\alpha]_D^{18}$ +59·5° (*c*, 1·8) (Found : C, 79·5; H, 11·0. $C_{32}H_{52}O_3$ requires C, 79·3; H, 10·8%).

(*b*) Acetylation of α-amyranonol-II (400 mg.) with pyridine and acetic anhydride gave α-amyranonyl-II acetate (380 mg.) as needles (from ethanol), m. p. 217° (sintering at 206°), $[\alpha]_D^{18}$ +59·3° (*c*, 2·2); a mixture with the specimen described under (*a*) showed no depression in m. p.

Grateful acknowledgment is made to The Carnegie Trust for the award of a scholarship (to S. U. R.).

THE ROYAL TECHNICAL COLLEGE, GLASGOW. [*Received, December 28th*, 1950.]

241. *Studies in Polymorphism. Part VI. A Further Investigation of the Linear Rate of Transformation of Monoclinic into Rhombic Sulphur.*

By Norman H. Hartshorne and Melville H. Roberts.

New measurements of the rate covering the range 0—80° afford strong evidence that the activation energy which determines the temperature coefficient of the reaction is of the same order as the heat of sublimation and not appreciably less than this as was formerly thought (Part V).

A possible reason for the very large pre-exponential factor (*ca.* $10^7 \cdot vd$) is discussed. This is based on a suggestion by Garner that the transformation can proceed within small homogeneous elements of volume, *e.g.*, mosaic blocks, with a much smaller activation energy than the heat of sublimation, but that the latter amount of energy is required to bridge the discontinuity between one such element and the next, and is the rate-controlling factor. This idea receives some support from observations under the microscope which show that the advance of the interface is spasmodic, the interface continually surging forward locally at a greater rate than the average rate of advance.

The microscopic study has also shown that when the interface crosses the boundary between two differently oriented monoclinic crystals, it does so without change of orientation of the rhombic phase. The transformation is thus essentially a process of crystal growth in a solid medium.

Part V of this series (*J.*, 1940, 588) described measurements of the linear rate of transformation of monoclinic into rhombic sulphur at 20°, 30°, and 40°. It had originally been intended to study the rate at temperatures up to the transition point, but the work had to be suspended.

The present paper describes new measurements covering the range 0—80°, and also gives the results of a study of the nature and mode of advance of the interface at different temperatures under the microscope. This work has shown that some modifications to the conclusions drawn in Part V are necessary. First, the extension of the study to lower temperatures has yielded strong evidence that the activation energy determining the temperature coefficient is of the same order as the latent heat of sublimation, and not appreciably less than this as was thought. Secondly, the microscopic examination of the polycrystalline films, which has now been done under conditions permitting interference figures to be obtained, has shown that crystals presenting *b*(010) sections are by no means the most common, and that several other orientations are frequently represented.

Some of this work has been briefly reported [*Discuss. Faraday Soc.*, 1949, No. 5 (Crystal Growth), p. 149] but no details were given.

Experimental.

The methods described in Part V were used for the purification and degassing of the sulphur, and for the preparation of the films of the monoclinic modification, which were confined as before in stepped glass–mica–glass cells * and covered the same range of thicknesses (0·06—0·10 mm.). The method of measuring the linear rate over the range 10—80° was also essentially the same, but the projection apparatus was completely rebuilt to a design which gave much greater rigidity and incorporated several modifications making for greater convenience in operation. The projection unit (lantern, thermostat, and projection lens) was mounted on a trolley constructed of heavy-gauge angle iron, and running on rails so that the magnification on the screen could be readily altered or adjusted. The thermostat with all its necessary equipment was mounted on rollers running on a pair of secondary rails fixed across the top of the main trolley, so that it could be drawn to one side out of the path of the light. This enabled the lantern and lens to be used by themselves for projecting photographic records of the sulphur films, which was the basis of the method of measurement used in studying the transformation at 0° (see later).

In the earlier work, the slides were contained in an air-tight cell placed inside a larger cell in the thermostat (Part V, Fig. 2). The air-tight cell was used because it seemed possible that the fall of velocity at constant temperature observed with other substances, and attributed primarily to the development of a gap at the interface owing to the difference in the densities of the two forms (Parts III and IV), might have been partly caused by loss of material from the interface by evaporation.

* In what follows, these cells with their sulphur films will be referred to simply as "slides."

Sulphur, however, showed no fall of velocity at all, and, as will appear later, there are strong reasons for thinking that this result was not connected with the fact that evaporation was prevented. Since also the double-cell arrangement was rather clumsy and inconvenient, and a slide placed in it took a long time to acquire the temperature of the thermostat (25—45 mins.), some modification of this part of the apparatus seemed desirable. Rough preliminary observations made on slides laid on a hot plate at 70° and 80° indicated that there was no significant difference in the mean rate of advance of the interface between slides that were completely unprotected and others on which the film edges were sealed with either a thick layer of sulphur or sealing wax. It was therefore decided that some relaxation of the precautions against evaporation could be accepted in the interests of greater convenience and an improved rate of heat transfer, and the following simplified design was adopted. A single cell of all-glass construction, having internal dimensions of $9 \times 1\frac{3}{4} \times \frac{1}{8}$ in., and with its open top ground flat, was firmly clamped at its upper end to a brass bridge running across the top of the thermostat. (The cell was specially made for this work by Messrs. C. J. Whilems, Barkingside, Essex.) At the bottom of the cell was placed a layer of a mixture of rhombic sulphur and calcium chloride in order to establish a dry atmosphere saturated with sulphur vapour. The slide was held by leaf springs in a very light box frame made of 50 : 50 nickel–iron alloy, and so constructed as to be a good sliding fit in the cell. (This alloy has approximately the same coefficient of expansion as glass, so there was no danger of fracture of the cell at higher temperatures.) At the top and to one side of the frame was attached a vertical brass tube which contained, and acted as guide for, the piano-wire handle of the inoculating brush, which was made and used in the same way as in the earlier apparatus. A further quantity of the sulphur–calcium chloride mixture, contained in a small flat box made of perforated zinc, was placed on top of the frame as it was being lowered into the cell. The upper end of the brass tube passed through a hole of the same diameter in a brass plate, faced underneath with rubber, which formed the lid of the cell and was bolted to it by means of suitably positioned screws and finger nuts after the frame had been inserted. A clamping screw passing through the edge of the plate, and bearing on the brass tube, enabled the vertical position of the frame in the cell to be adjusted. The top of the brass tube was kept closed by a small cork threaded over the projecting end of the wire handle of the inoculating brush, except when this was actually in use.

This slide holder proved to be very convenient to use at all temperatures, and it reduced the time equired for a slide to reach thermostat temperature to 15—20 minutes.

A further modification to the apparatus was the addition of a "Londex" timer, operated by a synchronous motor, to switch on the projection lamp at regular intervals. This timer could be set to make contacts of any required duration at intervals of $\frac{1}{4}$, 1, or 2 minutes. The timer was also arranged to operate an electromagnetic counter placed on the observation desk near the screen, so that the reading on the counter gave instantly the time for which the transformation had been in progress. This greatly facilitated the timing of the reaction—a particularly important consideration at the higher temperatures, where the more rapid movement of the interface demanded the most concentrated attention on the part of the observer. The counter readings were checked from time to time during an experiment against an accurate watch, so that any irregularity in the speed of the timer due to fluctuations in the mains frequency should not pass unnoticed. A master switch to the projection lamp was also mounted on the observation desk so that the lamp could be switched on for one or two seconds during an "off" period if the need arose to check any of the observations.

As in the previous work, the screen was ruled in vertical lines at distances apart equivalent to 0·25 mm. on the actual film, and horizontal lines at distances equivalent to 1·5 mm. divided the grid into 20 sections. The screen board was now, however, provided with vertical, lateral, and tilting adjustments by means of which the image of the edge of the film could be rapidly brought into coincidence with the zero vertical line at the start of an experiment. The time of crossing a vertical line in any section was taken, as before, as the mean of the time at which the image of the most forward part of the interface had just reached the line (time S) and that at which the most rearward part had just passed over the line (time F). On all slides the interface advance was followed to a distance of at least 1·5 mm. from the film edge, and in most cases to 2·0 mm. For reasons to be discussed later, the results obtained for the first 0·25 mm. were not used in calculating the mean rate.

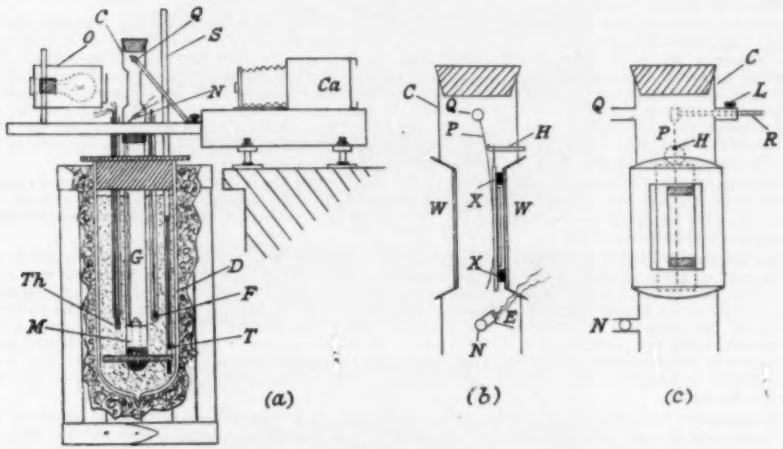
The method of timing varied somewhat at the different temperatures to suit the different rates. At 30° the projection lamp was switched on for 15 seconds at intervals of 1 minute, the S times being noted at the odd minutes and the F times at the even minutes. At 50° and 80° the lamp was switched on for 10 seconds at $\frac{1}{2}$-minute intervals (since the rate was appreciably greater than at 30°), and the S and F times were noted respectively at alternate periods of illumination. At these three temperatures it was possible by this procedure to keep track of the movement of the interface in all 20 sections without difficulty. In the work described in Part V, both S and F times were noted during every period of illumination, but these periods, though made as short as possible, were not constant, for the lamp was switched on by hand and was kept on as long as was needed to make the observations. The more regular timing given by the present method is obviously to be preferred on general grounds, and for the three temperatures in question, any error in the mean times introduced by taking S and F readings at alternate periods was negligible in comparison with the variance of the results. In any case the intervals between periods of illumination were half those in the previous work. At 60° and 70° the rate was near its maximum, and it was considered necessary to take both S and F readings together. It was not then possible to follow the movement in all 20 sections in the same run; at first only 5, and, with more practice, 8 sections could be dealt with. Each slide was therefore inoculated and studied in two separate halves, *i.e.*, half the slide was inoculated, and the movement of the interface followed in 8 sections, and then the other half of the slide was treated similarly. The periods of illumination were of 10 seconds at $\frac{1}{2}$-minute intervals.

At 10° the movement of the interface was too slow to be followed in the above manner, since it would have involved continual observation of the screen for 7—9 hours. The following method was

therefore adopted. The gridded screen was replaced by a sheet of drawing paper with a vertical line ruled on it. The screen board was adjusted so that the vertical line coincided with the image of the film edge, and the transformation started by inoculation in the usual manner. When the interface had advanced an actual distance of about 0·25 mm., its position was recorded on the drawing paper by tracing with a pencil. When it was estimated that the interface had advanced on the average about 1·5 mm. (between 7 and 9 hours), its position was traced again. Both tracings were made starting from the same end of the interface, and the times were taken as those at which the tracings were half completed. Twelve slides were studied in this way, giving a total length of interface equal to those studied at the higher temperatures. Each traced record was then divided into 20 horizontal sections of width equivalent to 1·5 mm. on the actual film, and the advance in each section, represented by the mean distance between the two pencil lines, was determined by means of a transparent scale. (The mean position of a line was taken as the average of its most forward and most rearward points.) Since the time interval between the two tracings varied somewhat from slide to slide, the results were multiplied by appropriate factors to convert them into values of the interface advance for a period of 10 hours. The results could then be averaged and treated statistically.

Since only the two tracings were made at 10°, the results did not enable a time–distance graph to be drawn for this temperature. Moreover, only 240 values of the rate (20 on each of the 12 slides) were obtained, as compared with about 1200 at other temperatures (though the same " area of transformation " was of course studied). Since, however, these results were the last to be obtained, and it was already known that the rate at both higher and lower temperatures was linear, it seemed unnecessary

FIG. 1.



to collect the data for a time–distance graph, whilst the number of values appeared to be adequate to give a satisfactory measure of the variance of the rate.

In all the above experiments heat rays from the projection lamp were absorbed by passing the beam through (1) a plate of Chance heat-absorbing glass placed between the lantern condenser and the thermostat, and (2) a 2% solution of copper sulphate contained in a glass cell in the thermostat. The residual heating effect of the beam on the sulphur films was tested by means of a slide in which a very small copper–constantan thermocouple (made by thinning down the wires with acid) was embedded in the sulphur. This slide when placed in the usual position in the slide holder, with the thermocouple at the centre of the beam, and exposed to the light at the intervals and for the periods given above, showed a maximum rise of temperature of 0·1° during illumination, and this could be regarded as negligible.

Measurements at 0°.—At this temperature the rate was extremely slow (1·5 mm. in about 50 hours), and neither of the methods described above would have been suitable. The principle of the method adopted was to store a number of previously inoculated slides in a vessel surrounded by an ice–water bath, withdraw and photograph them at 12 hour intervals, and subsequently project the negatives on to a gridded screen on which the successive positions of the interface could be read off. The apparatus is shown in Fig. 1; *G* was a wide glass tube containing calcium chloride at the bottom to maintain a dry atmosphere, and just above this was a rack *M* in which six slides could be supported in a vertical position. No precautions against evaporation were thought necessary at this low temperature. The slides used for this work differed slightly from those used at other temperatures in that they were built up, not from two 3 in. × 1 in. plates (microscope slides), but from one of these and a smaller plate measuring 2½ in. × ¾ in. The reason for this will appear later. Furthermore, each slide, before being placed in the apparatus, was inserted in a light frame made of copper foil, with a large wire ring soldered to the upper end. By engaging a hook on the end of a long rod with this ring, the slide could be lowered into its position in the rack *M* and also raised to be photographed (see later). The upper end of *G* was

attached by means of a wide rubber band to a metal tube *C* provided with glass windows on opposite sides (*W*, *W*, Fig. 1, *b*), and closed at the top with a rubber stopper as shown. In line with the windows were a 100-watt opal lamp in a metal housing *O*, carrying a filter of heat-absorbing glass, and a quarter-plate camera *Ca*. When it was required to photograph a slide, a current of dry nitrogen was passed through *C via* the side tubes *N* and *Q*, the stopper at the top was removed (the stream of nitrogen preventing the ingress of moist air), the long hooked rod, mentioned above, was passed down into *G*, and the slide was thereby raised (with the smaller of its two glass plates facing the camera) and hung on the bracket *H* by passing the wire ring over this (Fig. 1, *b* and *c*). The hooked rod was then removed, and the stopper replaced. The two ends of the larger plate of the slide were next brought into contact with the metal strips *X*, *X* by a gentle pressure of the spring wire *P* applied by turning the rod *R* and locking it with the screw *L*. (During the previous operations this rod had been drawn to one side, so that the spring wire did not interfere with the hanging up of the slide on the bracket *H*.) In this position the film of sulphur was in focus on the camera plate. When the photograph had been taken, the slide was lowered to its position in the rack *M* by reversing the above operations. The whole process of raising a slide, photographing it, and returning it to the rack took less than a minute. To facilitate the operation, the bottom of *G* was illuminated by means of the flash-lamp bulb *F* while it was in progress (Fig. 1, *a*).

The ice–water mixture surrounding *G* was contained in the large Dewar vessel *D*, which was embedded in slag wool in a large wooden drum. The top of the Dewar vessel was closed with a thick wooden cover in two halves, one of which could be easily removed for addition of fresh ice. Thermal insulation was very good, however, and replenishment was only needed at long intervals. The ice–water mixture was stirred from time to time with the hand stirrer *S*, the stem of which was hollow and contained a thermometer *T* which could be read when the stirrer was at the top of its stroke.

The Dewar vessel also contained two copper–constantan thermocouples *Th*, and a similar thermocouple was soldered to the slide rack *M*, the leads to it entering the apparatus through *E* (Fig. 1, *b*). By connecting the latter couple with one of those in the Dewar vessel, the rise of temperature of *M* resulting from the replacement of a slide after it had been photographed could be determined, the thermal E.M.F. being read on a sensitive galvanometer. This rise proved to be only about 0·5°, and the temperature returned to 0° in about 5 minutes. Even if the temperatures of other slides in the rack were affected to a like extent, it can be shown that the effect on their rates integrated over the whole run would be negligible. The zero of the galvanometer was checked from time to time by putting it in circuit with the two couples *Th* in the Dewar vessel.

The temperatures to which the slides rose during the brief and infrequent periods (see above) required to photograph them were not determined, but calculations show that the effect on the average rate for a run could not have exceeded about 3%, which is quite without significance for the estimation of the apparent activation energy to the nearest 1000 cals.

The window *W* (Fig. 1, *b*) nearer to the camera was masked (this is not shown in the figure) so that only a vertical strip of the sulphur film sufficiently wide to include comfortably the whole movement of the interface in a run was projected on to the photographic plate. The image of this strip registered with an opening of similar shape in a three-ply board forming the back of the camera. The dark slide containing the plate was held against this board by guides and leaf springs so that it could be shifted sideways to bring different sections of the plate opposite the opening. By means of this arrangement, eight records of successive positions of the interface could be taken on the same plate. Fig. 2 is a reproduction of a positive print of a typical negative. The comparatively regular advance of the interface will be noted.

To measure the advance, the negatives were projected by means of the optical system of the projection apparatus used for the higher temperatures on to a gridded screen ruled with vertical lines at a distance apart equivalent to 0·1 mm. on the actual film, and divided into horizontal sections equivalent to 1·5 mm. For this purpose the thermostat was drawn to one side out of the path of the light (see above) and the negative was supported in a special holder in front of the lantern condenser. This holder was a brass plate faced with baize, against which the gelatin side of the negative was lightly pressed by two large leaf springs. The light passed through an oblong opening in the middle of the plate, this opening being only large enough to illuminate one of the strip records on the negative at one time. The negative was moved in the holder so as to bring the eight records in sequence opposite the opening, correctly registered with respect to one another, and so that the image of the edge of the film coincided with the zero vertical line on the screen. This registration was facilitated by the presence of a mark on the step of the slide which had been made previously with Indian ink (see Fig. 2). Final adjustments were made by using the vertical, tilting, and lateral controls on the screen board, referred to above. For each record, the mean advance in each of the horizontal sections was taken as the average of the most forward and most rearward points on the interface as measured on the vertical scale lines. Estimates of these positions could be made to 0·05 mm. (actual). Thus the only difference in timing the reaction as compared with the procedure at higher temperatures was that here the measurements gave the linear advance in 12 hours, which averaged 0·345 mm., whereas at higher temperatures (except 10°) the measurements were times taken to advance by 0·25 mm. In both cases the width of of the horizontal sections was the same, namely 1·5 mm.

The method of starting a run at 0° was as follows. Six slides were prepared, and the monoclinic phase caused to crystallise, as in the work at higher temperatures. At intervals of 5 minutes each slide was inoculated by means of a brush of the same type as that used in the projection apparatus, and immediately lowered to its place in the rack *M*. Zero time was taken as the time of inoculation, but this was not important since, as in the work at higher temperatures, the first stage in the advance of the interface was ignored when calculating the mean rate.

Microscopic Study of the Transformation.—As indicated in Part V, the rather thick films used for the velocity determinations were not suitable for a complete optical study under the microscope. Owing

FIG. 2.

Photographic record of advance of interface at 0°. The arrows indicate the film edge. The rhombic phase appears dark.

To face p. 1109.

to the high birefringence of sulphur, films of this thickness between crossed Nicols gave only "high white" polarisation effects, necessitating the use of special compensators of high relative retardation for the recognition of the "fast" and "slow" directions, whilst the fact that the films were confined between two microscope slides prevented the use of objectives of high numerical aperture (and therefore small working distance) so that interference figures could not be obtained. Moreover the details of the manner in which the rhombic phase grows, which it was one of the main objects of the present investigation to study, are not easy to make out on a thick film owing to the small depth of focus of high power objectives.

The microscopic study was therefore carried out on films of the order of 0·01 mm. or less in thickness, prepared by melting a little sulphur between a slide and a cover slip. As with the thicker films, care was taken not to exceed 123° when doing this. Owing, however, to the greater rate of heat loss from the thinner films through the thin cover slips, it was necessary to modify the procedure for crystallising out the monoclinic form as follows, in order to avoid the formation of very small crystals. When the sulphur had melted, a microscope slide was placed over the preparation so as to cover all but one edge of the cover slip. After time had been allowed for the additional slide to become warm, the hot-plate temperature was lowered to about 115°, and a platinum point run along the uncovered edge. A good proportion of large crystals was thus obtained, many of which filled or nearly filled the field of the microscope when the $\frac{1}{2}$-inch objective was used (equivalent diameter about 0·3 mm.). Inoculation of these films was conveniently effected by running the corner of a razor blade covered with powdered rhombic sulphur along an edge. (The type of inoculating brush used with thicker films was too coarse to penetrate.)

For study of the interface movement at different temperatures, an electrically heated stage was used. This consisted of a circular brass plate, 3 in. in diameter and $\frac{1}{16}$ in. thick, recessed underneath over most of its area to a depth of $\frac{1}{16}$ in. to accommodate an evenly spaced nichrome-ribbon heating element wound on mica. At the centre of the plate was a hole for the passage of the light, tapering from $\frac{1}{4}$ in. diameter on the lower surface to $\frac{1}{8}$ in. at the top, so as to fit the convergent beam from the condenser. A copper–constantan thermocouple was screwed to the under-side of the plate as near as possible to the edge of the central hole. A circular sheet of mica covering the under-side of the plate, and attached to the edge of it by small screws kept the heating element and thermocouple leads in place when the stage was not in use. The whole assembly was attached directly to the stage of the microscope (a Swift "Lapidex") by finger screws passing through four equidistant holes near the periphery. These holes allowed a little lateral movement so that the hot stage could be centred (this being done by focusing on the central $\frac{1}{8}$ in. aperture, a low-power objective being used) before the screws were finally tightened. The heads of two adjacent screws were recessed to take a pair of stage clips. The leads from the heating element and thermocouple were led upwards to a small terminal panel fixed just in front of the microscope, leaving sufficient slack to permit the microscope stage to be turned through one complete revolution. The cold junction of the thermocouple circuit was kept at 0° in melting ice in a Dewar vessel, and the temperature was read to $\frac{1}{4}$° on a high-resistance millivoltmeter. This had been previously calibrated by observations on the melting of a series of substances of known m. p. in powder form placed between a slide and a cover slip. Different calibration graphs had to be used for the low-power and the $\frac{1}{2}$ in. objectives (the latter was the highest power used with the hot stage) for the close proximity of the latter to the object had a considerable cooling effect, and with it, the millivoltmeter reading corresponding to a given temperature was higher than when a low-power objective was used, the difference increasing with rise of temperature. From the smoothness of the calibration graphs and the reproducibility of m. p.s, the accuracy of the stage was found to be rather better than ± 1°.

The advantage of this type of hot stage was that owing to its small thickness ($\frac{1}{16}$ in. plus the thickness of the mica cover sheet) the slide was not raised very much above its normal position in relation to the condenser, so that interference figures could still be obtained, though with some slight sacrifice of numerical aperture. Its temperature could be rapidly altered, and yet readily held constant over long periods by hand control of a rheostat in the heating circuit.

Photomicrographs of the interface were taken by means of a Kodak 35-mm. camera. This was supported on a bridge between two rigid pillars, one on each side of the microscope, which were firmly secured to a wooden baseboard to which the microscope was clamped. The bridge was pivoted about one pillar and was clamped to the other. By releasing this clamp, therefore, the bridge could be swung out of the way, thus permitting ordinary visual observation down the microscope. Two procedures were used: (1) the subject having been found by direct observation, the bridge with the camera focused on infinity was rapidly swung into position, clamped, and the exposure made; (2) the ordinary microscope eyepiece was replaced by a viewing eyepiece attachment incorporating a half-reflecting prism, which could be moved out of the path of the light by a wire cable control. With this, the bridge and camera were in position from the start, and the subject was observed through the viewing eyepiece up to and if necessary during the moment of exposure. If the maximum intensity of illumination was required, as when photographing a fast-moving subject, the prism was thrown out of position just before opening the shutter. The viewing eyepiece attachment was supplied by Messrs. Cooke, Troughton and Simms, Ltd.

With this apparatus and a Cooke 48-watt high-intensity lamp as illuminant (with a heat-absorbing glass filter) records of the interface could be made at exposures as small as 1/200 sec., when using a $\frac{1}{2}$ in. objective and ordinary light. With crossed Nicols and the same objective, exposures of 1/50 to 1/25 sec. were required. Some interesting records of the movement of the interface were also made with a 16-mm. Ciné camera mounted on the bridge in place of the Kodak, and further work on this method of study of polymorphic transformations is in progress.

The Temperature at the Interface.—The transformation of monoclinic to rhombic sulphur is an exothermic process, and it was therefore considered necessary to try to ascertain whether under the

experimental conditions the temperature at the interface was significantly higher than the temperature of the thermostat. In this connection we acknowledge with gratitude the assistance of Dr. P. M. Davidson, of the Physics Department, University College of Swansea. On the basis of the accepted principles of heat flow in a solid medium, and taking account of the fact that a real solid is an assemblage of atomic oscillators and not a continuum, Davidson obtains the following expression for the temperature rise, θ, at a plane heat source of infinite length and finite width moving perpendicular to the plane, in a solid medium extending indefinitely in all directions :

$$\theta = \frac{Q}{\pi k}\left[\frac{D}{2}\left(1 - \ln\left(\frac{DV}{8K^2}\right) - 0{\cdot}5772\right)\right]$$

where Q is the heat generated by unit area of the plane per second, V is the linear velocity, k is the thermal conductivity of the medium, D is the width of the plane source, and $K^2 = k/(\text{spec. heat} \times \text{density})$ for the medium. The conditions in the sulphur films used for the rate measurements could be regarded as approximating to those just stated, because the width of the interface was very small in relation to its length, and (if it is taken as the thickness of the film *) did not exceed 1/10 to 1/20 of the thickness of the glass slides confining the sulphur. The expression was therefore applied on the assumption that the actual temperature rise would lie somewhere between that for an all-glass medium and that for an all-sulphur medium. The results for 70° (at which V is near its maximum) were : θ (all glass) = $0{\cdot}5 \times 10^{-3}$ °c. ; θ (all sulphur) = 10^{-2} °c. It thus appeared that the effect was negligibly small. However, it was thought desirable to check this conclusion independently, and the following experiment was therefore carried out. The mixture of sulphur and calcium chloride was removed from the bottom of the glass cell of the slide holder, and dry mercury poured in to a depth of about 1½ inches. A slide was prepared in the usual manner, inserted in the nickel–iron frame, and lowered into the cell until its lower end was just above the mercury surface. After it had attained the temperature of the thermostat, it was inoculated, and then lowered further so that the lower half was immersed in the mercury. This half was therefore surrounded by a considerable quantity of a medium of good thermal conductivity and capacity at the thermostat temperature, and conditions for the dissipation of the heat of transformation were optimum. After the interface in the non-immersed upper part of the slide was seen to have advanced about 1·5 mm., a tracing of this part was made on the screen. Immediately afterwards, the slide was withdrawn from the mercury, and a tracing of the position of the interface in the lower half made. No significant difference in the rates for the two halves as indicated by these tracings was found. The experiment was done at a bath temperature of 60°, *i.e.*, just below the temperature of maximum velocity where the heating effect should be most marked, and it was repeated twice with the same result.

Results and Discussion.

Table I and Fig. 3 give the average time (t)–distance (s) results (at 0°, time-average distance), including for completeness those reported in Part V (with some small corrections which a

Table I.

Time (t)–*distance* (s) *results.*

Temp.	s (mm.) at : / t (hrs.) =											
0°		12.		24.		36.		48.		60.		72.
		0·36		0·69		1·03		1·39		1·73		2·09
	Δs		*0·33*		*0·34*		*0·36*		*0·34*		*0·36*	
	t (mins.) at : / s (mm.) =	0·25.		0·50.		0·75.		1·00.		1·25.		1·50.		1·75.		2·00.
20 †		36·8		71·5		110·5		154·8		201·5		245·2				
	Δt		*34·7*		*39·0*		*44·3*		*46·7*		*43·7*					
30 †		17·2		37·6		54·5		73·5		93·8		112·0				
	Δt		*20·4*		*16·9*		*19·0*		*20·3*		*18·2*					
30		20·6		40·6		59·0		75·8		95·1		107·4		122·2		136·5
	Δt		*20·0*		*18·4*		*16·8*		*19·3*		*12·3*		14·8		14·3	
40 †		6·9		15·3		23·6		32·4		41·7		49·8				
	Δt		*8·4*		*8·3*		*8·8*		*9·3*		*8·1*					
50		5·55		10·55		15·10		19·35		23·60		27·70		31·85		36·00
	Δt		*5·00*		*4·55*		*4·25*		*4·25*		*4·10*		4·15		4·15	
60		4·40		7·90		11·10		14·15		17·20		20·15		22·95		25·65
	Δt		*3·50*		*3·20*		*3·05*		*3·05*		*2·95*		2·80		2·75	
70		4·65		7·95		11·15		14·05		17·00		19·90		22·80		25·60
	Δt		*3·30*		*3·20*		*2·90*		*2·95*		*2·90*		2·90		2·80	
80		24·8		37·8		48·7		58·6		68·1		77·3		84·7		93·9
	Δt		*13·0*		*10·9*		*9·9*		*9·5*		*9·2*		7·4		9·2	

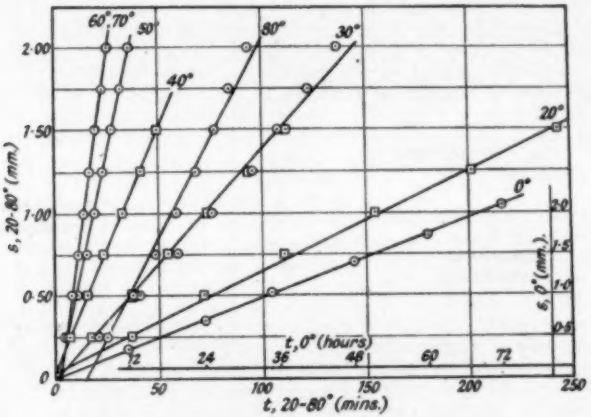
† Results of Elias, Hartshorne, and James, Part V.

* Actually it is effectively greater than this owing to the fact that the advancing front is wedge-shaped (see later), but the increase is not serious near the temperature of maximum V (at which θ is also a maximum), since the wedge is narrow in this region.

revision of the previous calculations of the means has shown to be necessary). Each figure in the present work is based on 230—240 measurements, except those for 12 and 24 hours at 0° (220 measurements each), and for 1·75 and 2·00 mm. at 80° (196 measurements each). No results for 10° are given here, since, as already stated, only the mean rate of advance from about 0·25 to 1·50 mm. was determined. Attention is directed to the close agreement between the old and the new results at 30° up to $s = 1{\cdot}50$ mm., beyond which the former did not extend. In view of the considerable variance of measurements of this nature, this may be regarded as very satisfactory.

All the plots for the new results (Fig. 3) are very near to straight lines, as was previously found at 20°, 30°, and 40°. From 50° to 80°, however, the " best " straight lines extrapolate to the t axis, the value of the intercept increasing with rise of temperature and being especially large at 80°. The marked initial increase in rate which this represents is succeeded at all these temperatures by a slight upward trend (see Δt values in Table I), and a similar trend is apparent in the new results at 30° if the Δt values for 1·75 and 2·00 mm. are taken into account. It was suggested in Part V that results for the first 0·25 mm. might be somewhat unreliable,

FIG. 3.



⊡ = *Results of Elias, Hartshorne, and James.*

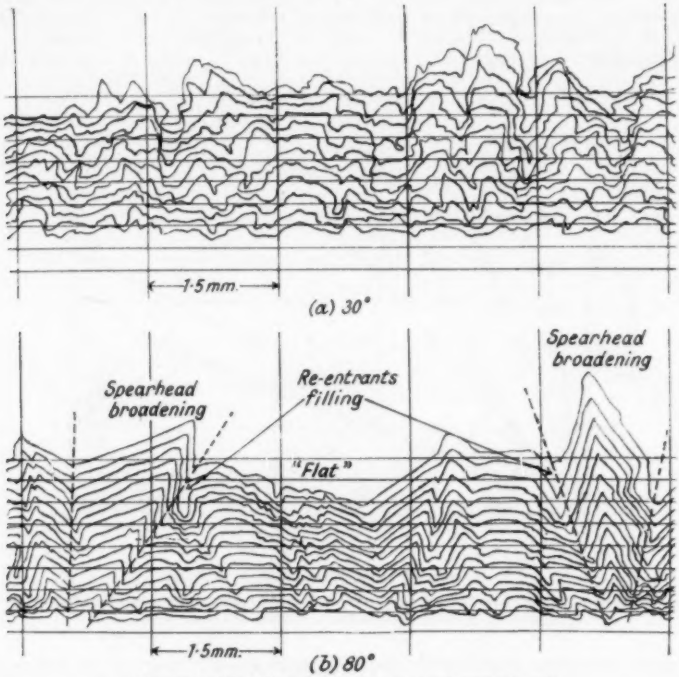
(The third point from the left on the 0° graph should be moved horizontally so as to be immediately above the 36-hour point on the time scale.)

but the reasons advanced were mostly such as would account only for an apparent initial *decrease* in the rate which was shown by the s–t graphs at 20° and 40° (see Fig. 3). (It may be noted that the s–t graph for the intermediate temperature of 30° extrapolates very nearly to the origin.) At first sight it seems possible that the deviations from linearity now in question might have arisen from the use of the new slide holder (p. 1098). This could not have completely prevented evaporation of the *monoclinic* form since the atmosphere inside the cell was saturated with vapour with respect to rhombic sulphur. If therefore loss of material from the film in the region of the interface did in some way slow down the rate of transformation, it would be expected that the effect would be most marked in the initial stages when the interface was very near to the film edge, and that it would increase with rise of temperature, as was actually found. The following experimental evidence and general considerations show, however, that evaporation could have had little if any effect on the rate except possibly in the very early stages.

(1) Films, very much thinner than those used for the rate measurements, prepared between a slide and cover slip and observed under the microscope at 60—70°, show no apparent reduction in the rate of advance of the interface when the cover slip is stripped off and the sulphur is thus completely exposed to the atmosphere. (If evaporation were important, it would be expected to affect conditions at the interface much more in these thinner films than in those used for the rate measurements.)

(2) If it be assumed that the thickness of the transitional layer at the interface is of the order of the average distance between the molecules in the crystals, *i.e.*, *ca.* 10^{-7} cm., then the interface " fissure " in a film 10^{-3} cm. thick, such as those used for the rate measurements, must be about 10^{5} times as deep as its distance from wall to wall, which is of course very much less than the average intermolecular distance in the free vapour (*ca.* $3{\cdot}5 \times 10^{-6}$ cm. at 80°). It seems impossible that diffusion from such a fissure could appreciably affect the population of molecules undergoing transition except near the film surfaces, especially when it is remembered that the walls are not inert but are continuous sources of these molecules, and that air is present. The rate of advance of the leading edge of the rhombic phase deep down in the film (which is what is observed) should not therefore be appreciably affected.

FIG. 4.

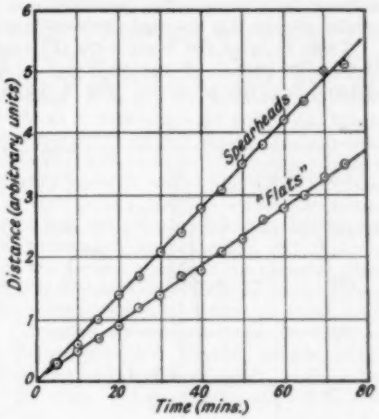


Tracings of position of interface at 5-minute intervals.

(3) At 80° the advancing rhombic phase consists of large crystals which may be broadly divided into two groups according to their orientation : (*a*) those whose leading edge is approximately parallel to the film edge (for convenience these will be referred to as " flats "); (*b*) more rapidly advancing " spearheads," most of which, to judge from their profile angles, are probably pyramids bounded by {111}, and if so, show that there is a preferred tendency to grow in the direction of the *c* crystallographic axis (see Fig. 4, *b*). Measurements of the average rate of advance of these flats and spearheads in a film have been made over the range 0·25—2·00 mm. (for the interface advance as a whole) from tracings of successive positions of the interface at 5-minute intervals. Fig. 4, *b* shows a section of these tracings. The rate is strictly constant, as will be seen from the very good straight lines in Fig. 5, which are based respectively on measurements made on 6 flats and 7 spearheads. This indicated that the advancing fronts of *individual crystals* do move at a steady rate, though the *s*–*t* results for the interface as a whole show an upward trend over the same range (Table I). If this latter had been due to evaporation becoming less and less important as the interface receded from the film edge, it should have appeared also in the measurements on the single crystals.

The observations just described suggest at least part of the reason for this upward trend. As the interface advances, the more rapidly moving spearheads broaden at the expense of the flats, and so contribute more and more to the average rate measured in the direction normal to the film edge. In addition, sharp re-entrants tend to fill up by lateral growth. Both these features are exemplified in Fig. 4, *b*. To a lesser extent the same features appear at lower temperatures, and could account for the upward trends observed at 50°, 60°, and 70°, and in the later stages at 30°. Only in the range above the temperature of maximum rate (about 65°, see later), however, do the spearheads show such good development as those illustrated in Fig. 4, *b*. Fig. 4, *a* shows for comparison tracings of the interface made at 30°. Spearheads are present, but it will be seen that they are not so large as those in Fig. 4, *b*, and that they do not maintain their individuality and direction nearly so well.

FIG. 5.



It is very doubtful whether the above explanation can account for the very much more marked increase in the rate observed in the initial stage at these higher temperatures—particularly that at 80°—and no good reason can be given for it. It is possible that evaporation of the monoclinic form at the edge of the film impaired the efficiency of the inoculation process by reducing the areas of contact between the monoclinic crystals and the particles of rhombic sulphur scattered by the inoculation brush, so that the continuous interface took longer to form and "get going." Indeed, we formed the impression that there was a distinct lag in the visible response to the act of inoculation at 80°, though it was difficult to be sure of this, because owing to refraction and internal reflection effects at the edge of the glass slide which coincided with the edge of the film, the latter could not be focused on the screen very critically. A contributing factor might be a phenomenon similar to the abnormally slow rate of growth of very small dehydration "nuclei" on crystals of salt hydrates, found, *e.g.*, by Garner and Cooper (*Trans. Faraday Soc.*, 1936, **32**, 1739), though it must be remembered that this effect decreases with rise of temperature, whilst that now in question increases.

TABLE II.

Mean linear rate (mm./hr.) calculated in different ways.

Temp.	(1.) Mode of distribution curve of Δt * values.			(2.) Mean of Δt values.			(3.) Mean of reciprocals of Δt values.		
	V_1.	log V_1.	Δ log V_1.	V_2.	log V_2.	Δ log V_2.	V_3.	log V_3.	Δ log V_3.
0°	0·028	−1·55		0·027	−1·57		0·029	−1·54	
			0·63			0·67			0·65
10	0·119	−0·92	0·48 } 1·11	0·126	−0·90	0·43 } 1·10	0·130	−0·89	0·45 } 1·10
20 †	0·36	−0·44		0·34	−0·47		0·36	−0·44	
			0·37			0·39			0·39
30 †	0·83	−0·08 }		0·79	−0·10 }		0·86	−0·07 }	
30	0·85	−0·07 }		0·86	−0·07 }		0·94	−0·03 }	
			0·34			0·33			0·35
40 †	1·83	0·26	0·29	1·75	0·24	0·29	1·98	0·30	0·26
50	3·53	0·55	0·18	3·39	0·53	0·15	3·60	0·56	0·15
60	5·36	0·73	0·02	4·77	0·68	0·01	5·16	0·71	0·01
70	5·66	0·75	0·56	4·92	0·69	0·53	5·30	0·72	0·52
80	1·54	0·19		1·43	0·16		1·60	0·20	

* Δt = Time required to advance 0·25 mm.
† Results of Elias, Hartshorne, and James, Part V.

The Temperature Coefficient of the Transformation.—As the basis for the comparison of the rates at different temperatures, only the results for the *s* range 0·25—1·50 mm. (italicised in Table I) have been used, except at 0°, thus eliminating the uncertainties attached to the measurements at the extreme edge of the film. Over this range the deviations from linearity are negligible or very small at all temperatures, and, as in Part V, the rate has been assumed to be constant in calculating the means from the Δt values. At 0° the measurements for the first

stage of advance from the film edge were again ignored, but the s range used, 0·36—2·09 mm., was necessarily rather different owing to the different method of measurement used. Since, however, the s–t graph for this temperature was a very good straight line over its whole length (see Fig. 3), this was not thought to be important. As stated above, about 1200 Δt values (Δs values at 0°) were averaged at each temperature. This corresponds to the same length and advance of interface as was covered by the results in Part V, but there the Δt values for the first 0·25 mm. were included in the means. The means have now been recalculated, without using these initial measurements, in order to make them comparable with the newer results, though this has made little difference in the figures.

Table II gives the linear rates (V) expressed as (1) the reciprocals of the modes of the Δt distribution curves, (2) the reciprocals of the means of the Δt values, and (3) the means of the reciprocals of the Δt values. Fig. 6 shows a typical Δt distribution curve. These curves were

FIG. 6.

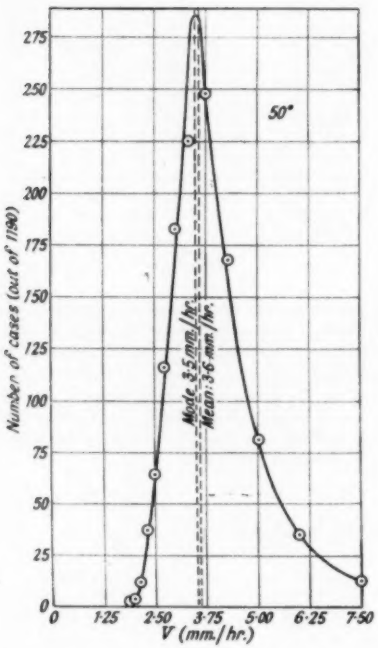
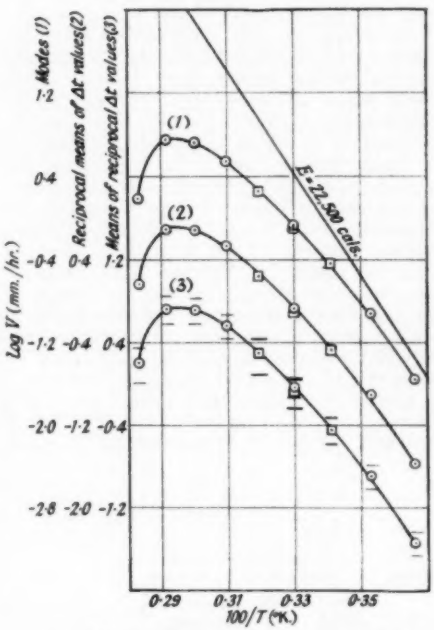


FIG. 7.



⊡ = *Results of Elias, Hartshorne, and James.*

the same at all temperatures in being skew towards the higher Δt values, and they exhibited no trend in the degree of skewness with change of temperature. The standard deviations and coefficients of variation have already been reported (*Discuss. Faraday Soc., loc. cit.*). Fig. 7 shows the plots of log V, expressed in the above three ways, against $1/T$. The standard deviations are shown on curve (3) by the short strokes above and below each point. It will be seen that, from the point of view of determining the temperature coefficient, particularly at the important low-temperature end of the curves, there is little to choose between them. This appears also from the Δ log V values in Table II. The closest agreement between the old and the new results at 30° is given by the modes (1), and this curve is also the smoothest, but the means of the reciprocal Δt values (3), *i.e.*, the means of the measured velocities, are probably the most fundamental functions of the results statistically.

The apparent activation energy (*i.e.*, the value corresponding to the slope of the log V–$1/T$ graph) over the limited range of temperature, 20—40°, covered in Part V was found to be practically constant at about 15,000 cals. The theoretical value for 20 to 30°, based on the

assumption that the rate was given by the difference between the rates of evaporation of the two forms (or between rates of escape having the same temperature dependence as these) was found by the graphical method described in Part IV (*J.*, 1938, 1636) to be about 22,000 cals. [A rounded value of 1000 cals. for q, the mean heat of transformation, was used in this calculation. Using the more accurate figure of 730 cals., and calculating by means of the equation

$$\ln V - \ln [1 - e^{q(1/T_s - 1/T)/R}] = -\frac{E\alpha}{RT} + \ln \frac{A\alpha}{2} \quad . \quad . \quad . \quad . \quad . \quad . \quad (i)$$

(see *Discuss. Faraday Soc., loc. cit.*, p. 150, eqn. 6), we obtain 19,400 cals. as the value for the range 20—40°—still very much greater than the experimental one.] It was concluded from this that the true activation energy involved in the transfer of molecules from the monoclinic to the rhombic lattice was less than the heat of sublimation. The newer results show, however, that this conclusion was premature, at least in so far as it concerned the activation energy which determines the temperature coefficient of the transformation (see later). The apparent activation energy for the lower range 0—20° is 20,300 cals. on the basis of the modes (Curve 1, Fig. 7), or 20,000 cals. on the basis of the means (Curves 2 and 3), whilst the value calculated for this range by means of eqn. (i) is 20,500 cals., in very good agreement with these figures. In the Faraday Society paper (*loc. cit.*) it was shown that deviations from the requirements of eqn. (i) at higher temperatures such as that just cited for the range 20—40°, could be quantitatively accounted for on the assumption that the surface energy of the rhombic phase below the temperature of maximum velocity was slightly higher than normal, as was suggested by microscopic studies of the interface. It was also pointed out that deviations attributable to this cause would be small at lower temperatures. The good agreement between the observed and the calculated apparent activation energies for the range 0—20°, when E_s is taken as the heat of sublimation of the monoclinic form, may therefore be taken as evidence that the true activation energy is equal to, or nearly as great as, that which a molecule must acquire to enter the free vapour phase (it can hardly be greater than this).

The fact that all the curves in Fig. 7 appear to tend to a limiting slope corresponding to *ca.* 22,500 cals. supports this conclusion irrespective of the particular mechanism by which the molecules are supposed to be transferred from one lattice to the other. Stated in quite general terms, the reason why the rate of transformation passes through a maximum is that there is an increasing tendency for the reverse reaction to occur, *i.e.*, for molecules to pass from the stable to the unstable lattice, as the transition point is approached. As the temperature falls, the relative contribution of this reverse flow to the net rate of transformation progressively decreases, so that the slope of the log rate–$1/T$ graph tends more and more to that corresponding to the activation energy for the forward reaction. In the theory underlying eqn. (i), the forward and the reverse reactions are pictured as simple evaporation–condensation processes occurring through a transitional layer; in Dunning's nucleation theory (*Discuss. Faraday Soc., loc. cit.*, p. 156), the reverse process is the overall tendency for nuclei below the critical size to disperse, some at least of the molecules so dispersed finding their way back to the unstable lattice.

Measurements of the rate at temperatures below 0° are required to settle definitely whether the curves are in fact approaching a limiting slope of the above value, and it is hoped to make such measurements in the near future.

In Part V the point was made that a direct comparison between scalar properties such as the heat of sublimation on the one hand, and activation energies derived from measurements of the linear rate of advance of the interface on the other, was not justifiable, since the measurements had a largely vectorial basis. This was based on the supposition that the monoclinic crystals were mostly oriented with b(010) parallel to the plane of the film, and their c axes parallel or nearly parallel to the direction of growth of the rhombic phase. As appears below, it is now known from microscopic examination that the orientation of the monoclinic crystals in the films is much more varied than this and that, owing to the ragged contour of the interface (particularly at the lower temperatures), a given rhombic crystal advances along many different crystallographic directions in the same monoclinic crystal. The rate measured may therefore be assumed to be the average for a large range of relative orientations of the two forms, and the point in question thus seems now to be of little importance.

Dunning's Theory of the Temperature Coefficient (*ibid.*, p. 157).—Further consideration has been given to this theory which appears to account so elegantly for the effect of temperature on the rate over the whole range studied. The objections previously advanced, however, still seem to be important, and in particular it is felt that a theory which fails to take account

of the obvious differences in the character of the interface above and below the temperature of maximum velocity must at best be incomplete. One of these objections, it will be recalled, was that the theory led to a value for the surface free energy which appeared to be far too small (4 ergs/cm.^{2}). It is of interest that the explanation proposed by the senior author for the deviations of the results from eqn. (i) (see above) is consistent with a much more probable value. The deviations up to 50—60° can be accounted for by a ϕ factor (ratio of the rate of escape of molecules from the finely serrated front of the rhombic phase to the rate for a plane surface) of 1·10. Taking the surface free energy as 100 ergs/cm.^{2}, which seems to be of the right order, since the value (International Critical Tables) for the liquid at the melting point is 60, and applying the Gibbs–Thomson equation, we find that this factor corresponds to a particle radius of between 10^{-5} and 10^{-4} cm. This is the order of the size of the smallest " teeth " visible under the microscope on the advancing front of the rhombic phase.

Moreover, it seems that there is no case on record of the growth of a real crystal from its free vapour obeying Volmer's equation for two-dimensional nucleation quantitatively, the critical supersaturation for continued growth being always very much less, if detectable at all, than the equation demands (cf. Volmer's own investigation of the growth of crystals of iodine, phosphorus, and naphthalene; Volmer and Schultze, *Z. physikal. Chem.*, **1931**, *A*, **156**, 1), and, as is well known, Frank (*Discuss. Faraday Soc.*, No. 5, p. 48) has accounted for this by the theory that real crystal faces have self-perpetuating growth steps due to screw dislocations.

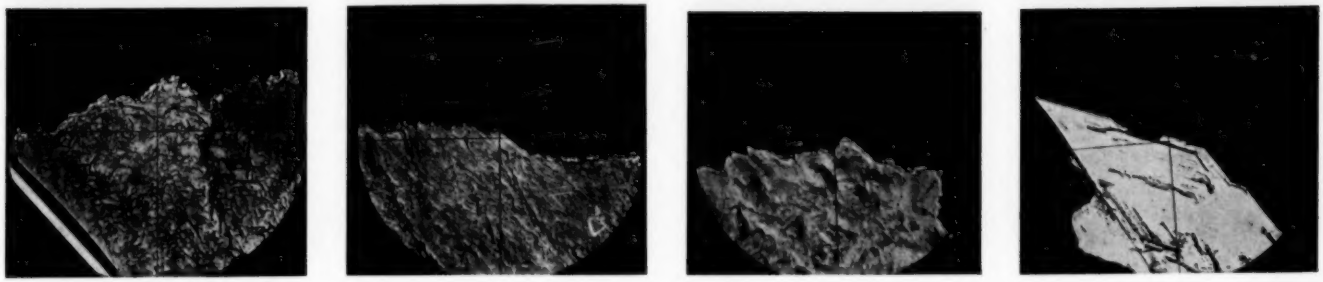
Specimens of Sulphur showing Abnormal Rates of Transformation.—During the measurements at 80° (the last temperature but one at which measurements were made), the stock of purified sulphur (A) which had been used up to then became nearly exhausted, and a new one (B) was prepared, exactly the same methods of recrystallisation and degassing being used as before. Slides prepared from this sample and studied at 80° behaved in a highly unusual manner. After advancing at about the normal rate for the first 0·25 mm., the interface developed a number of promontories which advanced at rates up to some 10 times the normal value, at the same time spreading sideways into the screen sections occupied by the more slowly moving parts. The sample of sulphur was again recrystallised and degassed, but slides prepared from this new product (C) showed the same abnormal behaviour. So too did slides prepared from a third sample of recrystallised and degassed sulphur (D) derived from an entirely different source of starting material, which in all cases was " Crystalline Sulphur " supplied by either Hopkin and Williams or British Drug Houses.

Various tests were made to ascertain whether this behaviour was due to the presence of impurities (*e.g.*, selenium), or to a high proportion of insoluble sulphur (which must be formed to some extent when the sulphur is melted in the degassing process), but the results were all negative or inconclusive. It was then noticed that specimens B, C, and D consisted of clear crystals, whilst A consisted of opaque lumps. This indicated that the former had crystallised from the melt directly as the rhombic form, the latter as the monoclinic form which had then undergone the usual transformation to the rhombic form. Specimen D was therefore put through the degassing process again, but in such a way as to ensure that it crystallised initially as monoclinic tulphur. (The specimen was melted except for a few crystals, which at that high temperature underwent transformation to the monoclinic form, and on cooling induced the crystallisation of this form alone.) After time had been allowed for the cooled specimen (E) to be transformed into rhombic sulphur, slides were prepared from it and these behaved in an entirely " normal " manner, *i.e.*, in each slide the interface advanced at approximately the same rate over its whole length, and the mean rates at 80° covered almost exactly the same range as did those for slides prepared from specimen A at this temperature. Specimen E was subsequently used for the measurements at 10°, and Fig. 7 shows that the results fit in well with those at 0° and 20°.

Comparisons of the melting behaviour of specimens B, C, and D with that of specimens A and E have since been made on the hot stage (previously described) under the microscope, and, to the accuracy possible with this apparatus (see above), show no evidence of any difference of chemical purity: B, C, and D all melted completely at about 115° (the metastable m. p. of rhombic sulphur), but most of the opaque particles of A and E were seen to undergo a phase transformation above the monoclinic–rhombic transition point (96°) and then melted at about 120° (the m. p. of monoclinic sulphur). Further, when B, C, and D were caused to crystallise from a melted film as monoclinic sulphur, this melted at the same temperature as A and E, whilst if the latter were crystallised from the melt in the rhombic form they melted at the same temperature as the original particles of B, C, and D.

The only ascertainable difference then between the " abnormal " specimens and specimens

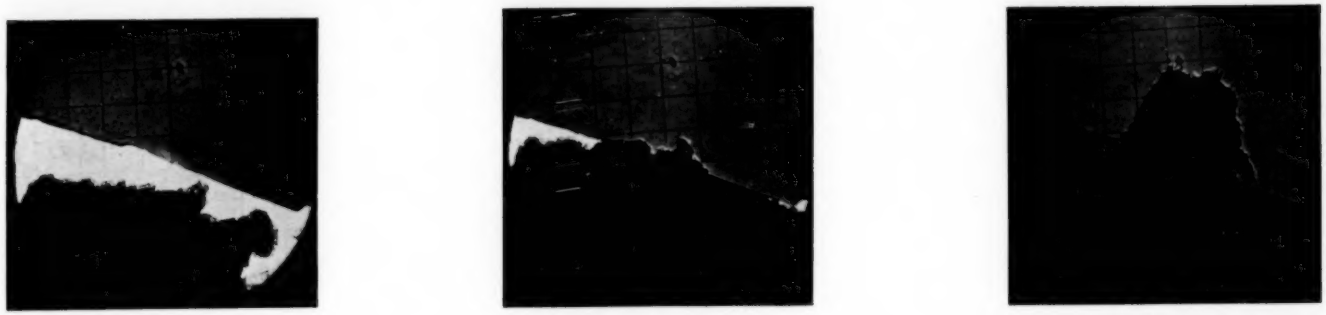
FIG. 8.



(*a*) 20°. (*b*) 40°. (*c*) 60°. (*d*) 80°.

Effect of temperature on the interface. (*The monoclinic phase is shown in extinction.*) *Scale* × 185.

FIG. 9.



(*a*) (*b*) (*c*)

Interface crossing the boundary between two monoclinic crystals. (1 *grid square* = 0·023 *mm.*)

To face p. 1109.

A and E was that, when heated, A and E underwent transformation at the transition point (presumably because they consisted of a mass of small crystals, the large specific surface of which favoured the formation of nuclei) and melted at the stable m. p., whereas the former did not do so and melted some 5° lower. Why this should have led to such a profound difference in the mode of transformation of the monoclinic films prepared from these melts is not clear and further investigation is required. Possibly the reason is to be sought in a difference in the mosaic structure, or other type of crystal imperfection (see p. 1113). A less likely explanation is that the " abnormal " films contained some γ-sulphur (one of the monotropic monoclinic modifications, commonly called " nacreous " sulphur). This sometimes appears when a thin film between a slide and a cover slip is allowed to crystallise spontaneously, though usually only when the supercooling is great, and we have observed that, when it is inoculated with rhombic sulphur, the interface advances much more rapidly than in ordinary monoclinic (β) sulphur. We have also noticed, however, that γ- changes very rapidly into β-sulphur at about 80° when the two are present in the same film, and it therefore seems very unlikely that, if the former had appeared in the films prepared for the rate measurements, it would have survived the period in the thermostat before inoculation.

Microscopic Study of the Advance of the Interface.—It must be said at once that the details of the manner in which the rhombic phase advances as revealed by high-power microscopy are very complex and varied, and merit a much closer study than has been made so far. New information is being sought by application of the cinephotomicrographic technique. The main results of microscopic study obtained up to the present are as follows. Except where otherwise stated, they refer to observations made on very much thinner films than those used for the rate measurements. The reasons for using thinner films have already been given (p. 1101).

(1) The interface advances, not as a plane wall normal to the plane of the film, but as a wedge which penetrates the monoclinic phase. Between crossed Nicols and with the stage turned so that the monoclinic phase is in extinction, this wedge is clearly revealed by bands of polarisation colours running parallel to the interface and rising in Newton's scale from the leading edge to the body of the rhombic phase. In monochrome, these bands of colours may be seen in the photomicrographs in Figs. 8, *a*, *b*, and *c*. Very considerable variations in the width of this wedge-shaped fringe were observed at different parts of the interface in the same film, and at temperatures below 40° it was often much wider than the examples shown in the photomicrographs. In general, however, the fringe was narrower the higher the temperature.

The observed widths of the fringe in relation to the order of thickness of the films are not inconsistent with the supposition that the wedge surfaces correspond to crystal faces of low indices (though very imperfect ones at the lower temperatures), except perhaps in the case of the greatest widths (about 0·05 mm.; order of film thickness, 0·01 mm.). Owing to the relatively large *c* spacing of rhombic sulphur ($a = 10{\cdot}34$, $b = 12{\cdot}92$, $c = 24{\cdot}55$ A.; Warren and Burwell, *J. Chem. Physics*, 1935, **3**, 6), very acute-angled forms commonly occur. Thus the internal angle between opposite {111} faces on the same pyramid is only about 37°, and a growth front bounded by these faces would show a very pronouncedly wedge-shaped contour. Above the temperature of maximum velocity, the surfaces of the narrow wedges seen on the borders of the well-developed crystals that are formed in this range are more certainly recognisable as definite crystal faces. Thus the width of the narrow wedge running along the top edge of the spearhead in Fig. 8, *d* (80°) is about 0·003 mm. Assuming that the film is 0·01 mm. thick, and that the leading edge of the wedge lies on the lower glass surface, we have that $\tan^{-1} 0{\cdot}01/0{\cdot}003 = 73°$, which is the wedge angle and also the polar angle between the upper surface of the wedge and the plane of the spearhead. This is equal to the angle (111) : ($1\bar{1}1$) (Groth, " Chemische Kristallographie," Vol. I), and the measured profile angle of the spearhead, 36°, agrees almost exactly with that calculated from Groth's data for a (111) face on an unmodified pyramid. Although the close agreement between the estimate of the wedge angle and the angle (111) : ($1\bar{1}1$) must to some extent be fortuitous in view of the approximate nature of the values for the wedge width and film thickness, it does suggest strongly that the wedge surface is a (111) face, and this is supported by the cleavage cracks seen in the figure to be running parallel to the wedge (with others parallel to the concealed face along the lower edge of the spearhead), for rhombic sulphur is known to have a (111) cleavage.

The marked variations in the width of the wedge observed in different parts of the same film at lower temperatures could, on the above basis, be due to the differing orientations of the rhombic phase along the interface. Unfortunately, it has not yet proved possible to trace any such relation, owing to the difficulty of obtaining clear interference figures from the rhombic

phase in this region (see below). The very wide wedges referred to above may possibly arise through the interface advancing preferentially along cleavage cracks in the monoclinic phase that are parallel to the *plane of the film*. Some support for this possibility comes from one of our cinephotomicrographic records, which at one stage shows two apparently independent interfaces advancing at different levels in the film. This kind of transformation is already known to occur in (001) tablets of yellow mercuric iodide (Kohlschütter, *Kolloid-Beih.*, 1927, **24**, 319) and splits them into leaflets parallel to the (001) cleavage.

The wedge-shaped fringe appears just as prominently in films from which the cover slip has been stripped, and also in flakes which have been completely detached from the slide by gentle scratching with a needle. It is not therefore due in any way to the presence of the glass surfaces between which the films are normally confined.

(2) As seen in fine detail, the advance of the interface over any small element of its length exhibits continual and spasmodic fluctuations of rate arising from (*a*) local small-scale surges of growth, and (*b*) the formation of cracks due to the shrinkage attending the transformation, which hinder the advance to a greater or less degree. The surges are of three kinds : (i) the sudden protrusion of small promontories at the leading edge of the wedge ; (ii) the rapid spreading of layers along this edge ; (iii) the rapid spreading of layers over the surface of the wedge. These layers recall those described by Bunn and Emmett (*Discuss. Faraday Soc.*, No. 5, *loc. cit.*, p. 119), which are seen on crystals of certain substances growing from strongly supersaturated solutions. The size of the promontories is variable, but their diameter is commonly of the order of 10^{-4} cm. or less (approaching the limit of resolution of the microscope), and at lower temperatures they appear to be very rounded. The finer serrations on the interface in Fig. 8, *a* are typical of the appearance of the larger ones. The layers spreading along the edge of the wedge are about 10^{-3} to 10^{-4} cm. thick.

It should be explained that these rapid movements are superimposed on what appears to be a steady advance of the leading edge of the wedge ; *i.e.*, between two successive surges at the same part of the interface, movement does not stop but proceeds smoothly (or appears to do so within the limits imposed by the resolution of the microscope) at a lower rate.

It is very difficult to compare accurately the relative contributions of the three kinds of surge at different temperatures by visual observation alone, because of the differences in the average rates of advance of the interface as a whole. At the lower temperatures events succeed one another so slowly that they are apt to be missed ; at higher temperatures everything happens so quickly that the eye cannot take it all in. The further application of the cinephotomicrographic technique will, it is hoped, resolve this difficulty, and also enable the local rates of the advance to be measured. The results of visual observation and of the study of the few cinephotomicrographic records made so far are as follows. At room temperature, the leading edge of the interface advances in the main steadily, but very small rounded promontories push ahead continually at frequent intervals along the length (see Fig. 8, *a*). Sharp re-entrants between two closely neighbouring promontories soon fill up by lateral growth. Occasionally, a thick layer spreads across the surface of the wedge. As the temperature rises, the promontories become progressively more " crystalline " in contour, and an increasing proportion of the interface consists of straight lengths (see, *e.g.*, that at the middle of Fig. 8, *b*). Along these straight sections layers are seen to travel, these layers originating from promontories formed at one end or the other. At 60—70°, where the average rate is a maximum, the interface has lost almost completely the finely serrated contour characteristic of the lower temperatures, and consists of straight or nearly straight sections, along which layers spread in rapid sequence both along the leading edge of the wedge and over its surface, the latter moving from the body of the rhombic phase towards the leading edge, but not possessing the regular and parallel contours of those observed by Bunn and Emmett (*loc. cit.*) on crystals growing from solution. A close study of the mode of advance of the interface at still higher temperatures has not yet been made, but from preliminary observations the well-formed crystals (Fig. 8, *d*) appear to grow by a combination of a steady forward movement and the spreading of layers along the leading edge.

The cracks which form as a result of the shrinkage attending the transformation (referred to hereafter as " growth cracks ") may be classified into (*a*) short cracks along the leading edge of the interface, (*b*) short cracks parallel to the interface and just behind it, and (*c*) cracks which start in the rhombic phase and then penetrate through the interface a little way into the monoclinic phase. At lower temperatures all these cracks are irregular and often strongly curved, and it is not possible to trace any relation between their directions and the extinction directions of the rhombic phase, as would be the case if they formed along definite cleavage planes.

Fig. 8, *a* illustrates their varying shapes and directions. As the temperature rises and the crystallinity of the rhombic phase increases, the cracks become straighter and obviously tend to form more and more along definite cleavage planes. Thus the cracks parallel to the edges of the spearhead in Fig. 8, *d* may be identified as the traces of (111) cleavages (see above).

Growth cracks of type (*a*) halt the advance of the interface temporarily where they form. The advance is resumed either as the result of growth spreading around the ends of the crack, as is seen happening at the large crack in the upper part of Fig. 8, *d*, or because there is a " bridge " somewhere along the crack (*i.e.*, the crack is incomplete at some point) over which growth can continue. Cracks of type (*b*) have no apparent effect on the rate of advance, and those of type (*c*) only hinder the advance if they are inclined to the advancing front, or curve round so as to run approximately parallel to it. Such cracks often continue to open up ahead of the interface as it advances, for some considerable distance.

In addition to these growth cracks there are also present in the films a considerable number of what will be called " thermal cracks," which form when the monoclinic crystals are cooling after the film has been prepared, owing to the unequal coefficients of expansion of sulphur and glass. In thin films as used for the microscopic work, these thermal cracks can be seen to pass right through the film and they form complete barriers to the advance of the interface where they are parallel to it. The interface at the ends of such a crack, however, spreads inwards and joins up as in the case of growth cracks (*a*) and thus advance ahead of the crack is resumed.

These thermal cracks were also present, of course, in the thicker films used for the rate measurements, and it might be thought that they had an important effect on the average rate. Microscopic examination of a number of slides undergoing transformation showed, however, that this was not so. In the first place only those cracks which were parallel or nearly parallel to the film edge were potential barriers of any importance. A crack which is normal or much inclined to the edge offers little or no hindrance to the advance; the interface travels along each side of it. Secondly, many of the cracks in these thicker films appeared not to pass right through, for the interface crossed them without hesitation. Thirdly, the cracks were all short in relation to the length of interface studied, and were usually spaced in the direction of growth at intervals greater than their length. Thus when a barrier crack parallel to the film edge was encountered, the advance continued on either side and spread inwards to fill the area in front of the crack. Calculation shows that, this inward spreading being assumed to proceed with the same velocity in all directions (*i.e.*, the spreading fronts are arcs of circles—a reasonable assumption for the average behaviour in a large number of crystals), 95·7% of the area in front of the crack * will have been filled up by the time the interface on either side has advanced a distance equal to the length of the crack. The microscopic examination also showed that, at any time, less than 20% of the length of the interface was held up by barrier cracks, so their effect on the time taken to reach a given grid line would be proportionally reduced. Still less would be the effect on the *difference* between the times to reach two successive grid lines, *i.e.*, on the Δt values. In any case, the hindrance due to these thermal cracks would not be expected to vary appreciably with temperature, so the effect on the temperature coefficient should be negligible.

(3) The interference figures presented by the monoclinic crystals in the thin films show that the orientations relative to the plane of the films (and presumably this applies also to the thicker films used for the rate measurements) are much more varied than was thought when Part V was written. The frequent occurrence of extinction angles near to the maximum value of 44° led at the time to the conclusion that *b*(010) was the favoured orientation. In monoclinic sulphur, however, the optic axial plane is parallel to *b*(010), and $2V$ is fairly large (*ca.* 58°). This combination of optical properties results in an initially very slow decline in the extinction angle relative to *c* as the section changes from (010) towards (100). Thus the extinction angle for (110) which is inclined at about 45° (polar) to (010) is 38°, and even for (210) [64° to (010)] it is as high as 29°. Moreover, (001) sections with edges defined by (110) faces show an extinction angle of about 45°.

In addition to (010), which is often seen but is by no means the most frequent orientation, we now find that (100), (001), (110), and (210) are commonly present, as was found by Gaubert (*Bull. Soc. franç. Min.*, 1905, **28**, 157). In addition, (101) has been observed, and also another (*h*0*l*) section, the indices of which have not been identified, but which is recognisable by its nearly centred optic axial figure. Moreover, elongations along all three crystallographic axes occur.

* *I.e.*, the area which would have been transformed if the crack had not been present.

The orientations of the rhombic crystals could not in general be determined with certainty. At lower temperatures, areas of the rhombic phase 0·2—0·3 mm. or more in diameter extinguished as a whole between crossed Nicols, and it was possible to determine their " fast " and " slow " directions, but they were extremely " fuzzy " in appearance (probably each such area was a crudely oriented aggregate of very small crystals), and they mostly gave poor interference figures. At higher temperatures where the crystallinity was better, it was possible to recognise (111) pyramids by their profile angles and (111) cleavage (*e.g.*, Fig. 8, *d*), but even here the interference figures were frequently obscure, and so the attempt to make a systematic study was abandoned.

Fraenkel and Goez's statement (*Z. anorg. Chem.*, 1925, **144**, 45) that one crystal direction of the monoclinic system is preserved in rhombic crystals resulting from transformation has not been substantiated by our observations. Indeed, no definite relation between the orientations of the two phases on either side of the interface was found to exist, and the reason for this is apparent from (4) below. In 50 cases studied to investigate this point, however, evidence was found that the relative orientations were not completely random. In these cases the mean angle between the " slow " directions of the two forms was 32°, whereas for random, orientation it should be 45°. A statistical test shows that the chance that this difference was a random sampling error is less than 0·1%.

(4) The most important result so far obtained from the microscopic study of the transformation is that *when the interface crosses a boundary between two differently oriented monoclinic crystals there is no change in the orientation of the rhombic phase.* This is illustrated by the example shown in Figs. 9, *a*, *b*, and *c*, photographed between crossed Nicols. In *a*, the interface with the rhombic phase in extinction is seen advancing towards the boundary between two monoclinic crystals, the different orientations of which are apparent from the fact that the upper one is nearly in extinction, and the lower one is not. In *b*, the interface has gained a bridgehead at a place where the two monoclinic crystals are in contact, and in *c* it is well across. There is, however, no departure from extinction after crossing, and therefore no change in orientation.

This result shows that the transformation process is essentially one of crystal growth in a solid medium. Molecules from the unstable phase are added to a pattern already laid down, *i.e.*, the stable crystal, as in the growth of crystals from fluid isotropic media. The orientation of the unstable phase does not influence that of the growing crystal once this is established, though it may influence the rate of growth. This latter point remains to be investigated.

The orientation of the unstable phase may, however, govern the orientation of a nucleus that starts spontaneously within it, and it may have been an observation of this kind which led Fraenkel and Goez to make the statement referred to above. An attempt has been made to investigate this possibility by a study of the nuclei which form spontaneously in films that have been remelted (see Part V, p. 591), but so far without success. The difficulty has been that very few of these nuclei appear in thin films, and by the time one has been noticed it has been found to have grown over several monoclinic crystals, so that it is impossible to say in which one it was generated. On general grounds it seems very probable that such an initial orientational relationship does exist, but if so, the indications of it to be found in a polycrystalline film will decline with the number of crystal boundaries crossed by the interface. The significant departure from random orientation in the 50 cases mentioned above (in all of which the interface had travelled some distance into the film) may perhaps be taken as evidence that there was a definite relationship at least in some crystals at the film edge where nucleation was effected. (In artificial nucleation by the methods used in this work, it is to be expected that some of the monoclinic crystals will be " touched off " by mechanical shock with a result similar to that of spontaneous nucleation, and not by contact with the particles of rhombic dust scattered by the inoculating device.)

The Temperature-independent Factor.—In the Faraday Society Discussion (*loc. cit.*) the suggestion was made by the senior author that the large temperature-independent factor of the transformation (*ca.* 10^7 times the product of the vibration frequency and the lattice spacing) could be explained by a " trigger " mechanism analogous to that proposed independently by Burgers and Mott (*Proc. K. Ned. Akad. Wet.*, 1947, **50**, 719) to account for a similar discrepancy in the rate of recrystallisation of metals. The fact that there is no change of orientation of the rhombic phase on crossing a crystal boundary which was not then known, is, however, strongly opposed to this idea. It means that molecules in the course of their transfer from the monoclinic to the rhombic lattice must be free to adopt whatever orientations are demanded for a continued build-up of the latter. The trigger mechanism on the other hand implies that the removal of one mole-

cule from a mosaic block by thermal activation enables a rearrangement to the stable pattern to sweep through the block, as though the one molecule has been acting as a sort of keystone propping up the unstable edifice. If this were so, it would surely mean that there would be a definite spatial relationship between the new and the old patterns, so that when the interface passed from one crystal to another which was differently oriented, there would be a sharp change in the orientation of the rhombic phase, and this does not occur.

At the same Discussion, Garner (*loc. cit.*, p. 194) put forward an alternative explanation of the large temperature-independent factor, based on studies of the linear rate of growth of dehydration nuclei on chrome alum crystals, which shows a similar anomaly, and this explanation has been further developed in private correspondence with the senior author. Briefly, it is to the effect that the reaction can proceed with a small activation energy and therefore rapidly over small homogeneous elements of volume such as mosaic blocks, but that periodically the interface encounters obstacles which may be either cracks at mosaic block boundaries or growth cracks resulting from shrinkage. The passage of such an obstacle requires the formation of a bridge across it, and this will necessitate a large activation energy, which, if the bridge is formed by the condensation of vapour molecules in the crack, will be of the same order as the heat of sublimation. This large activation energy will determine the temperature coefficient of the reaction. This picture avoids the difficulty associated with the trigger theory discussed above, for the bridge would be a continuation of the pattern of the rhombic phase.

Let the width of the homogeneous blocks in the direction of advance of the interface be w cm., the width of the intervening cracks being assumed to be negligible in comparison. Further, let the rate of advance within a block be $\nu d e^{-a/RT}$, where ν is the vibration frequency of the molecules in the monoclinic lattice, d is the average spacing in this lattice, and a is the activation energy, which is a small quantity, or at least considerably smaller than the heat of sublimation, since it is supposed that within the block the molecules can take up their positions on the rhombic lattice without having to escape completely from the attractive field of the monoclinic lattice (*e.g.*, by executing small rotational movements). If E is the activation energy for bridge formation (of the same order as the heat of sublimation; see above), then the time taken to form a bridge may be put equal to $Ke^{E/RT}$ secs., where K is a constant. The number of block-crack pairs in 1 cm. is $1/w$, and therefore the time taken to advance 1 cm. is

$$\frac{1}{w}\left(\frac{we^{a/RT}}{\nu d} + Ke^{E/RT}\right) = \frac{e^{a/RT} + (\nu d/w)Ke^{E/RT}}{\nu d} \text{ secs.}$$

or the rate is

$$\frac{\nu d}{e^{a/RT} + (\nu d/w)Ke^{E/RT}} \text{ cm./sec.}$$

If a is sufficiently small compared with E, the first term in the denominator is negligible in comparison with the second, and the expression for the rate simplifies to $(w/K)e^{-E/RT}$. If we take w as the order of the width of a mosaic block, 10^{-5} cm., and E as 22,500 cals., K at 0° (rate = 0·029 mm./hr.; see Table II) works out to 10^{-17} sec. This seems to suggest that the vibration frequency of the molecules in the lattice from which the bridge is formed is at least as great as 10^{17}, whereas the usual estimate is 10^{12}—10^{13} for the mean frequency. A discrepancy of about this order, 10^4, has however been found by R. S. Bradley (personal communication; paper in the press) between the observed rate of evaporation of crystals of rhombic sulphur, and the rate calculated from the equation $\nu d e^{-L/RT}$, where L is the heat of sublimation, so the above value of K probably does not constitute an important objection to the theory. Of course, if the homogeneous blocks are larger than has been assumed above, *e.g.*, if they are the regions between the visible growth cracks, K will be proportionally increased.

Calculation shows that if $E = 22{,}500$ cals., a can be as great as 10,000 cals. without affecting the validity of the approximation that the rate $= (w/K)e^{-E/RT}$. Thus the theory allows for quite a large amount of energy for the transformation within the homogeneous blocks.

In the above treatment, no account has been taken of the reverse reaction, and the expressions as they stand are therefore only applicable to temperatures far below the transition point. They may be made general by multiplying by $(1 - \phi e^{R(1/T_0 - 1/T)/R})$, if eqn. (i) is taken as the theoretical basis, or by $e^{-A''/RT}$, where A'' is the activation energy for two-dimensional nucleation, if Dunning's nucleation theory be accepted. On the latter theory, the two-dimensional nucleus would itself constitute the bridge across the crack, if the width of the latter were of the order of a single lattice spacing.

The general idea that the reaction proceeds by a series of rapid sweeps over small elements of volume is supported by the spasmodic character of the advance of the interface which is

revealed by microscopic examination as described above. A closer test of the theory must however, await the more detailed measurements of the local rates of advance, which it is hoped to carry out by means of the cinephotomicrographic technique.

One of us (M. H. R.) desires to thank the Department of Scientific and Industrial Research for a Maintenance Grant during the course of this investigation. Acknowledgments are also due to the Chemical Society for a Research Grant, and to Imperial Chemical Industries Limited for the loan of a polarising microscope. We are also greatly indebted to Professor W. E. Garner, F.R.S., for the suggestion just discussed and for his interest in the work, and to Mr. R. S. Bradley for many helpful comments and criticisms.

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242. *Eight- and Higher-membered Ring Compounds. Part IV. Di-m-xylylene, Tri-p-xylylene, and New Syntheses of Pyrene and of Coronene.*

By WILSON BAKER, J. F. W. MCOMIE, and MISS J. M. NORMAN.

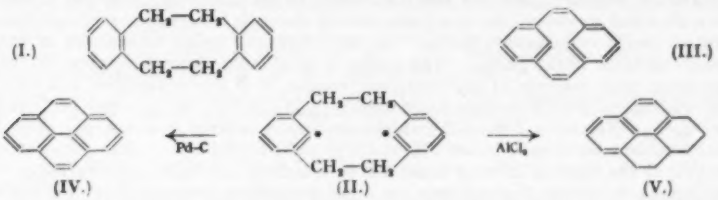
m-Xylylene dibromide reacts with sodium to give di-*m*-xylylene (II) containing a ten-membered ring, thus confirming earlier work of Pellegrin. Di-*m*-xylylene is dehydrogenated to pyrene (IV) in 60% yield when heated with palladium–charcoal, and is isomerised to 1 : 2 : 2*a* : 3 : 4 : 5-hexahydropyrene (V) when treated with aluminium chloride. *p*-Xylylene dihalides react with sodium to give a mixture containing tri-*p*-xylylene (VII) and *p*-di-(2-*p*-tolylethyl)benzene (VIII). The former, containing an eighteen-membered ring, is a novel type of molecule with three linear sides, and is converted into coronene (IX) in 1·9% yield when heated with palladium oxide. The stereochemistry of di-*m*- and of tri-*p*-xylylene is discussed.

THE main idea underlying this series of papers, set out in Part I (Baker, McOmie, and Ollis, *J.*, 1951, 200), was briefly a general investigation of the formation of eight- and higher-membered ring systems, in which a number of atoms forming part of the chain undergoing cyclisation are combined in a rigid group or groups, thereby diminishing the rotational possibilities and increasing the chance of cyclisation. This " rigid-group principle " has been applied in the formation of *s*-dibenz*ocyclo*octadiene (I) (Baker, Banks, Lyon, and Mann, *J.*, 1945, 27) from *o*-xylylene dibromide by reaction with sodium, and was illustrated more strikingly in Parts II and III (Baker, Ollis, and Zealley, *J.*, 1951, 201; Baker, Gilbert, Ollis, and Zealley, *J.*, 1951, 209) by the formation of large-ring anhydro-compounds derived from salicylic and cresotic acids. Thus, salicylic acid gives the eight-membered *cis*-disalicylide, the twelve-membered trisalicylide, the sixteen-membered tetrasalicylide, and the twenty-four-membered hexasalicylide.

The application of the " rigid-group principle " to *m*- and *p*-disubstituted benzenes, referred to in Part I, forms the subject of this communication; the results in the *meta*-series have been briefly reported elsewhere (*Chem. and Ind.*, 1950, 77). It was decided to work in the hydrocarbon series and to employ the Würtz–Fittig synthesis because (1) this reaction had proved successful in the preparation of *s*-dibenz*ocyclo*octadiene (I); (2) the compounds would be stable, thus allowing a variety of techniques for their isolation; and (3) the ethylene bridges would allow less steric interference between interior, benzenoid CH groups (*e.g.*, those marked with asterisks in formula II) than would occur in the shorter –CO–O– or –CO–NH– bridges in the corresponding cyclic anhydro-derivatives of phenolic acids or aromatic amino-acids. The reaction between *m*-xylylene dibromide and sodium had been previously investigated by Pellegrin (*Rec. Trav. chim.*, 1899, **18**, 458), but no work had been carried out in the *para*-series.

Di-m-Xylylene and its Conversion into Pyrene.—Pellegrin heated a mixture of *m*-xylylene dibromide (1 mol.) and bromobenzene (2 mols.) with sodium in ether and isolated diphenyl, a very variable yield (0—18% of crude product) of a hydrocarbon, m. p. 131·5°, of which the analysis and molecular weight established the formula $C_{16}H_{16}$, and a smaller quantity of a third hydrocarbon, $C_{16}H_{12}$, m. p. 191°. The compound $C_{16}H_{16}$, which yielded a dibromo-derivative $C_{16}H_{14}Br_2$, was regarded as di-*m*-xylylene (II), and to the compound $C_{16}H_{12}$, which showed unsaturated properties, was assigned the related diolefinic structure (III). Attempts to effect oxidative degradation of the hydrocarbon $C_{16}H_{16}$ were unsuccessful. Reinvestigation of this

reaction has shown that the hydrocarbon $C_{16}H_{16}$, for which we find m. p. 132—133°, may be isolated in the pure state in 12% yield after heating *m*-xylylene dibromide in anhydrous ether



with powdered sodium and a small quantity only of bromobenzene and sodium iodide. The last two substances act catalytically; the sodium iodide brings about an increased yield of the hydrocarbon but is not essential. In dioxan the yield fell to 6%; in ether the reaction was unsuccessful when the sodium was replaced by potassium, a liquid sodium–potassium alloy, lithium, or phenyl-lithium. An Ullmann-type reaction with copper bronze in the absence of a solvent was also ineffective. In no case did we find the hydrocarbon $C_{16}H_{18}$, m. p. 191°.

The formula (II) assigned by Pellegrin to the hydrocarbon $C_{16}H_{16}$ has, in spite of its stereochemically unfavourable structure, proved to be correct. This has been established by the fact that, when heated with palladium–charcoal, best in an open tube at 270—310°, it undergoes cyclodehydrogenation with loss of six atoms of hydrogen and bridging of the ten-membered ring to give the fully aromatic hydrocarbon pyrene (IV) in 60% yield. The pyrene was isolated as its picrate, from which it was regenerated. This very simple production of pyrene in a three-stage synthesis from *m*-xylene proceeds in an overall yield of 2·4%, but no attempt has been made to improve the yield of pure *m*-xylylene dibromide normally obtained (*ca.* 35%, not allowing for recovered *m*-xylene) by bromination of *m*-xylene.

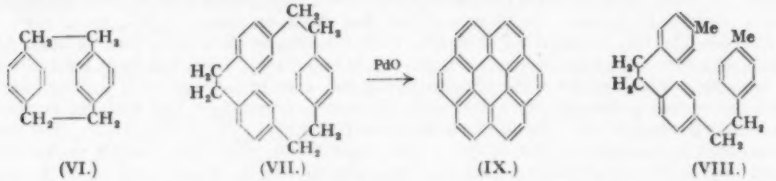
Dehydrogenation and ring-closure to polycyclic aromatic hydrocarbons have been effected in a number of cases by means of aluminium chloride (see, *e.g.*, Scholl and Seer, *Ber.*, 1910, **43**, 2202; Ruzicka and Hösli, *Helv. Chim. Acta*, 1934, **17**, 470; Buu-Hoï, *J. Org. Chem.*, 1949, **14**, 1031), but the reaction took an unexpected course with di-*m*-xylylene (II), giving the isomeric 1 : 2 : 2*a* : 3 : 4 : 5-hexahydropyrene (V) which was characterised as its picrate.

Models of di-*m*-xylylene show that this mobile molecule may take up three main forms, (1) a step-like *trans*-form in which the benzene rings are arranged in parallel planes separated by about 1·7 A., (2) two identical *cis*-forms with benzene rings inclined at an angle of about 60°, and (3) a twisted form through which the *cis*-forms pass during interconversion. These correspond closely with the forms of *s*-dibenzo*cyclo*octadiene illustrated in the paper by Baker, Banks, Lyon, and Mann (*J.*, 1945, 27) by Figs. 1, 1*B*, and 1*A*. If the molecule (II) possessed the normal bond angles and bond lengths, then the marked carbon atoms would be separated by a maximum distance of about 1·8 A. in the *trans*- and *cis*-forms. Since the minimum distance between non-bonded aromatic CH groups would normally be expected to be of the order of 4 A., it is clear that considerable strain must be present in (II), and the most probable form of the molecule appears to be a somewhat distorted *trans*-form. It is interesting to note that Brown and Farthing (*Nature*, 1949, **164**, 915) have shown that di-*p*-xylylene (VI) is produced in very small quantity from *p*-xylene at high temperatures. In this remarkable compound four pairs of non-bonded benzenoid CH groups would be expected to be separated by only 1·55 A., but *X*-ray examination has shown that, owing to distortion of the benzene rings, this distance is, in fact, increased to 3·09 A., which may be taken as possibly the minimum for non-bonded aromatic CH groups. It is evident that the total strain involved in increasing the distance between the carbon atoms marked • in (II) from 1·8 to 3·09 A. is not prohibitive, but we consider it unlikely that the hydrocarbon, m. p. 191°, obtained by Pellegrin has the formula (III), which represents a considerably more strained molecule. Di-*m*-xylylene contains benzene rings bridged in the *meta*-positions by chains of seven carbon atoms; the smallest *m*-bridges appear to be those containing six methylene groups which have been prepared by Prelog from nitromalondialdeyde and *cyclo*nonanone (see *J.*, 1950, 420).

In our original note (*Chem. and Ind.*, 1950, 77) we suggested that pyrene in coal tar may arise, in part at least, by synthesis from *m*-xylene, and this could occur either *via* di-*m*-xylylene, or *via* 2 : 6 : 2′ : 6′-tetramethyldiphenyl. We now find that traces of pyrene have been obtained from mixed xylenes at about 700° (Bradley and Parr, *Chem. Met. Eng.*, 1922, **27**, 737), though there is no indication of the intermediate steps, and the synthesis of pyrene described in this

paper is the simplest though not the most convenient, that has been achieved (see Elsevier "Encyclopædia of Organic Chemistry," Vol. XIV, p. 376).

Tri-p-xylylene and its Conversion into Coronene.—In investigating the action of sodium on *p*-xylylene dihalides, it was not thought probable that di-*p*-xylylene (VI) would be produced, and the simplest cyclic compound expected was tri-*p*-xylylene (VII), containing a triangular arrangement of three linear groups. The action of sodium on either *p*-xylylene dibromide or dichloride gave much material of high molecular weight, 1 : 2-di-*p*-tolylethane, and a difficultly separable mixture of *p*-di-(2-*p*-tolylethyl)benzene, $C_{34}H_{34}$ (VIII), m. p. 140—141°, and tri-*p*-xylylene, $C_{24}H_{24}$ (VII), m. p. 166—167°, which were finally isolated in a state of purity, though with considerable loss, in just under 5% and 4% yield respectively. The presence of di-*p*-xylylene (VI) in the reaction mixture could not be detected, and Brown and Farthing (*loc. cit.*) were also unable to isolate di-*p*-xylylene (or other crystalline products) from the material of high molecular weight which they obtained in a similar reaction. Substances (VII) and (VIII) were separated by fractional distillation under diminished pressure followed by fractional crystallisation from ethanol; chromatographic methods, fractional sublimation under diminished pressure, and co-distillation with ethylene glycol were not effective.



(VI.) (VII.) (IX.) (VIII.)

The structures (VII) and (VIII) assigned to the hydrocarbons of m. p. 166—167° and 140—141°, which show no properties due to unsaturation, are based on analysis and molecular-weight determinations, and on the fact that the first, like dibenzyl, showed no infra-red absorption band at 1380 cm.$^{-1}$ characteristic of the methyl group, whilst the second, like 1 : 2-di-*p*-tolylethane, did exhibit absorption at this wave-length. Neither (VII) nor (VIII) was attacked under the Kuhn–Roth conditions for estimation of *C*-methyl groups. Further evidence in support of the cyclic structure (VII) for the hydrocarbon of m. p. 166—167° has been obtained by dehydrogenation and oxidation with palladium monoxide at 360°; this brings about triple bridging of the eighteen-membered ring and dehydrogenation of the three dimethylene groups with production of coronene (IX) in 1·9% yield. This experiment was carried out with pure tri-*p*-xylylene, and the coronene was isolated as its picrate, regenerated therefrom on an alumina column, and identified by an *X*-ray powder photograph. A similar experiment with *p*-di-(2-*p*-tolylethyl)benzene (VIII) gave no trace of coronene. The dehydrogenation of (VII) to coronene is difficult and was attempted without success by treatment with palladium–charcoal, palladium–strontium carbonate, and selenium. The action of aluminium chloride on (VII) in carbon disulphide gave a trace of a picrate-forming, coronene-like compound. This synthesis of coronene from *p*-xylene by a three-stage process is by far the simplest which has been achieved, but it is scarcely of a practicable nature. The separate yields, *ca.* 60%, 4%, and 1·9%, give an overall of only about 0·05%, and the last two stages are not adaptable to large-scale work (cf. the coronene synthesis described in the succeeding paper).

Unlike di-*m*-xylylene (II), the molecule of tri-*p*-xylylene (VII) should be strainless because the three benzene rings can take up positions inclined to the general plane of the eighteen-membered ring, thus avoiding interference between non-bonded aromatic CH groups.

Tri-*p*-xylylene is a *para*-bridged benzene derivative, and contains fourteen carbon atoms in the bridge. Other *para*-bridged structures are known, recent examples being di-*p*-xylylene (VI) with an eight-membered bridge, and a compound containing a ten-membered hydroxy-ketone bridge prepared by the acyloin reaction (Kelley, MacDonald, and Weisner, *Nature*, 1950, **166**, 225).

Experimental.

M. p.s are uncorrected. Analyses are by Drs. Weiler and Strauss, Oxford, and Mr. W. M. Eno, Bristol.

Reaction of m-*Xylylene Dibromide with Sodium. Di-*m*-xylylene* (II).—A solution of *m*-xylylene dibromide (26 g.; m. p. 78—79°; prepared by the method of Ruggli, Bussemaker, and Müller, *Helv. Chim. Acta*, 1935, **18**, 616, and recrystallised from light petroleum, b. p. 60—80°) in anhydrous ether

(200 c.c.) was added to powdered sodium (10 g.) and, after the addition of sodium iodide (0·5 g.) and bromobenzene (1 c.c.), the mixture was boiled under reflux and continuously stirred (mercury-sealed stirrer). After the first hour a blue colour appeared and deposition of solid began; the reaction appeared to be complete after 18 hours. The cooled solution was then filtered, and distillation of the ether left a viscous oil which partly crystallised on storage; after crystallising four times from ethanol di-*m*-xylylene (1·2 g., 11·7%) was obtained in rhombic prisms, m. p. 132—133° [Found: C, 91·9; H, 7·8%; *M* (Rast), 200. Calc. for $C_{16}H_{16}$: C, 92·25; H, 7·75%; *M*, 208]. This compound did not decolorise a solution of potassium permanganate in acetone, nor did it combine with bromine.

Dehydrogenation of Di-m-*xylylene* (II) *to Pyrene* (IV).—A 30% palladium–charcoal catalyst was prepared from norite charcoal previously heated with 10% nitric acid for 6 hours. To palladium chloride (2 g.) dissolved in water (12 c.c.) and concentrated hydrochloric acid (1·2 c.c.), 40% aqueous formaldehyde (12 g.) and charcoal (2·7 g.) were added at 0°, followed by potassium hydroxide (12 g.) in water (12 c.c.). After ½ hour's heating at 60° the catalyst was collected, washed thoroughly with hot water, and dried at 100°.

Di-*m*-xylylene (II) (200 mg.) intimately mixed with the catalyst (300 mg.) was placed in an open tube (20 × 0·9 cm.), covered with a layer of catalyst (200 mg.), and heated for 6 hours in a metal-bath, the temperature of which was gradually raised from 270° to 310°. Repeated extraction of the contents of the tube with benzene yielded a colourless crystalline solid (162 mg.) which, when treated in alcoholic solution with picric acid, gave long, thin, orange-red prisms of a picrate (202 mg.) having m. p. 222° after crystallisation from alcohol (Found: N, 9·6. Calc. for $C_{16}H_{16},C_6H_3O_7N_3$: N, 9·75%). This was indistinguishable from authentic pyrene picrate (m. p. 223°) and the mixed m. p. was 223°. The filtrate from the picrate formation yielded unchanged di-*m*-xylylene, m. p. 132—133° (40 mg.). The yield of pyrene as picrate, after allowing for recovered di-*m*-xylylene, is 60%.

Pyrene was regenerated by shaking the picrate with ether and aqueous sodium carbonate, the ethereal layer yielding colourless, stout, rhombic prisms, m. p. 149°; when mixed with pure pyrene (m. p. 150°) it gave m. p. 149—150° (Found: C, 95·3; H, 5·2. Calc. for $C_{16}H_{10}$: C, 95·0; H, 5·0%).

Cycloisomerisation of Di-m-*xylylene to* 1 : 2 : 2*a* : 3 : 4 : 5-*Hexahydropyrene* (V).—Di-*m*-xylylene (100 mg.) was heated under reflux for 3 hours with carbon disulphide (5 c.c.) and anhydrous aluminium chloride (500 mg.), water was added, and the whole was extracted with chloroform. The residue left after removal of the solvents was sublimed at about 130°/17 mm., giving a pale yellow solid (52·5 mg.), which, after recrystallisation from alcohol, was converted into an orange picrate, m. p. 147—148°, by treatment with alcoholic picric acid. Decomposition of the picrate on an alumina column and elution with alcohol gave the hexahydropyrene (V) as colourless plates, m. p. 103—105°, from dilute alcohol (Found: C, 92·0; H, 7·7. Calc. for $C_{16}H_{16}$: C, 92·25; H, 7·75%). Cook and Hewett (*J.*, 1933, 404) give m. p. 147·5—148° for the picrate of this hexahydropyrene, and 105—105·5° for the hydrocarbon itself; *s*-hexahydropyrene has m. p. 132—133° (see also E. A. Coulson, *J.*, 1937, 1298).

Reaction of p-*Xylylene Dibromide and* p-*Xylylene Dichloride with Sodium. Isolation of* 1 : 2-*Di*-p-*tolylethane*, p-*Di*-(2-p-*tolylethyl*)*benzene* (VIII), *and Tri*-p-*xylylene* (VII).—(*a*) *p*-Xylylene dibromide [26 g.; m. p. 141—143°; prepared according to Atkinson and Thorpe, *J.*, 1907, **91**, 1698, Titley, *J.*, 1926, 514, and recrystallised from light petroleum (b. p. 60—80°)] in dioxan (200 c.c.; purified and freshly distilled over sodium) was added to powdered sodium (10 g.) and heated under reflux with the addition of sodium iodide (0·5 g.) and efficient mechanical stirring (mercury-sealed stirrer). As the b. p. was reached, a blue colour developed and a very vigorous reaction set in, necessitating the removal of the source of heat for a short time; the mixture was then boiled and stirred for a further 8 hours, then filtered, and the filtrate evaporated, leaving a product (6·2 g.) which crystallised on storage. (*b*) A similar product was obtained when parallel experiments were performed using (1) *p*-xylylene dichloride [17 g. (equiv. to 26 g. of *p*-xylylene dibromide), m. p. 97—99°; Kulka, *Canad. J. Res.*, 1945, **23**, *B*, 106], dioxan (300 c.c.), sodium (10 g.), and sodium iodide (0·5 g.) (yield of dioxan-soluble product, 5·3 g.), and (2) *p*-xylylene dichloride (17 g.), dioxan (900 c.c.; less vigorous reaction), sodium (10 g.), and sodium iodide (0·5 g.) (yield of dioxan-soluble product, 5·6 g.).

Mixed crude material (9 g.) from these experiments was distilled through a 4-cm. column at 0·2 mm. pressure, and the following fractions were collected: (1) b. p. <120°, m. p. 76—82°, 1·8 g.; (2) b. p. 170—185°, m. p. 100—123°, 1·2 g.; (3) b. p. 185—200°, m. p. 110—145°, 1·3 g.; (4) b. p. 195—215°, 0·6 g. Fraction (1) was recrystallised from ethanol, giving thin, irregular flakes, m. p. 78—81°; a mixed m. p. with an authentic specimen of 1 : 2-di-*p*-tolylethane, m. p. 81—82°, was 79—81°. Crystallisation from ethanol of fraction (2) gave a mixture of long, prismatic needles (*A*) and fine, white crystals; fraction (3) similarly gave some needles and irregular, stellate, crystalline aggregates (*B*); and fraction (4) gave mainly the stellate aggregates (*B*). By repeated crystallisation from ethanol, and by taking advantage of the fact that the prismatic needles formed rapidly on cooling, thus permitting the decantation of the mother-liquor before deposition of the other more slowly-separating product, there were finally obtained in the pure state 0·61 g. of (*A*) and 0·76 g. of (*B*).

Tri-p-*xylylene* (VII) (*A*) has m. p. 166—167° (Found: C, 92·1; H, 7·8%; *M*, ebullioscopic in benzene, 317. $C_{24}H_{24}$ requires C, 92·3; H, 7·8%; *M*, 312). The prisms frequently show feather-like, parallel growth. They do not reduce potassium permanganate.

p-*Di*-(2-p-*tolylethyl*)*benzene* (VIII) (*B*) has m. p. 140—141° (Found: C, 91·2; H, 8·8%; *M*, ebullioscopic in benzene, 318. $C_{24}H_{26}$ requires C, 91·7; H, 8·3%; *M*, 314).

Conversion of Tri-p-*xylylene* (VII) *into Coronene* (IX).—Pure tri-*p*-xylylene (VII) (50 mg.) mixed with palladium oxide (120 mg.) was heated in a sealed tube for 84 hours, the temperature being slowly raised from 280° to 380°, and the opened tube was dried in an evacuated desiccator and extracted six times with boiling toluene. The filtered toluene solution gave a residue which was sublimed at 200° rising to 300°/20 mm.; the sublimate (2·5 mg.) was dissolved in benzene and treated with alcoholic

picric acid, the red needles of a picrate which separated were dissolved in benzene, and the solution was passed through an alumina column, which was finally eluted with benzene. When concentrated to a small bulk the benzene solution gave bright yellow needles which were recrystallised from benzene (final yield, 0·9 mg.). This material and its picrate were indistinguishable from coronene and coronene picrate, and complete identity of the hydrocarbons was established by an *X*-ray powder photograph which showed complete coincidence of all lines, which were also of the same relative intensities.

The authors thank the Department of Scientific and Industrial Research for a maintenance allowance (awarded to J. M. N.), Mr. L. N. Short of Oxford for the infra-red determinations, and Dr. H. F. Kay of the H. H. Wills Physical Laboratory of this University for the *X*-ray powder photographs.

THE UNIVERSITY, BRISTOL. [*Received, January 25th*, 1951.]

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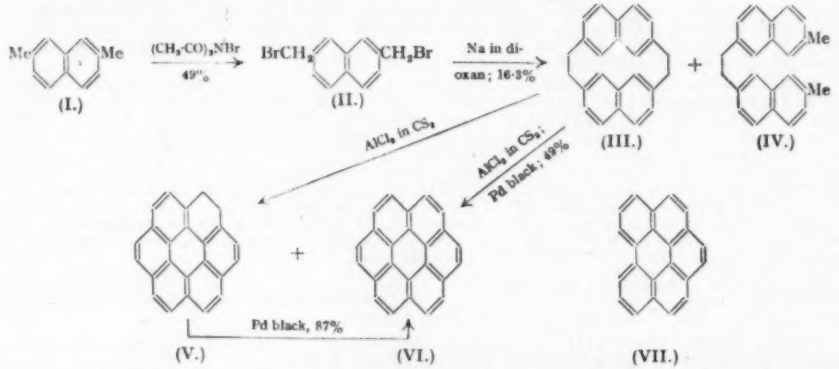
243. *Eight- and Higher-membered Ring Compounds. Part V. Di(naphthalene-2 : 7-dimethylene) and its Conversion into Coronene.*

By WILSON BAKER, F. GLOCKLING, and J. F. W. MCOMIE.

2 : 7-Bisbromomethylnaphthalene (II), prepared by bromination of 2 : 7-dimethylnaphthalene (I) with *N*-bromosuccinimide, reacts with sodium to give the fourteen-membered cyclic compound di(naphthalene-2 : 7-dimethylene) (III). Catalytic dehydrogenation of (III) gives a trace of coronene (VI), but with aluminium chloride in carbon disulphide at the boiling point it gives in good yield a mixture of 1 : 2-dihydrocoronene (V) and coronene. The 1 : 2-dihydrocoronene is dehydrogenated by palladium, giving coronene in 87% yield. The yield of pure coronene obtainable from (III) is 49%, or 4% from 2 : 7-dimethylnaphthalene.

THE preceding paper described the reaction of *m*-xylylene dibromide with sodium to give di-*m*-xylylene, and the catalytic dehydrogenation of this ten-membered *meta*-bridged benzene derivative to the tetra-cyclic aromatic hydrocarbon pyrene. In a preliminary note (Baker, McOmie, and Norman, *Chem. and Ind.*, 1950, 77) it was suggested that a similar series of reactions starting from 2 : 7-dimethylnaphthalene (I) should lead to coronene (VI), and the present communication records a successful and practicable synthesis of coronene along these lines. Our work was facilitated by a generous gift, from L. Light and Company, Limited, of 75 g. of 2 : 7-dimethylnaphthalene. This compound has been isolated from coal-tar, and is preparable by a nine-stage synthesis starting from *p*-toluidine (Bailey, Bryant, Hancock, Morell, and Smith, *J. Inst. Petroleum*, 1947, **33**, 523), the overall yield from that compound being about 20% (calculated on the maximum yields given in the literature).



2 : 7-Dimethylnaphthalene (I) was converted by pure *N*-bromosuccinimide in carbon tetrachloride in presence of benzoyl peroxide into 2 : 7-bisbromomethylnaphthalene (II), the yield being 49%. The possibility of nuclear bromination having occurred was excluded by the formation of a bisthiuronium bromide. In addition to (II) was isolated 2-bromomethyl-7-

methylnaphthalene, a compound previously prepared in a similar manner by Buu-Hoï and Lecocq (*J.*, 1946, 830), who, however, did not isolate the bisbromomethyl derivative. The action of sodium on 2 : 7-bisbromomethylnaphthalene in dioxan in the presence of sodium iodide gave dioxan-insoluble polymeric material and a mixture consisting mainly of two colourless, saturated compounds, the separation of which was effected by fractional sublimation at low pressures, crystallisation from benzene, and hand-sorting. One of the compounds, the desired di(naphthalene-2 : 7-dimethylene) (III), was obtained in a yield of 16·3%. The other, 1 : 2-di-(7-methyl-2-naphthyl)ethane (IV), isolated in 4·3% yield, has been formed as the result of both a Würtz–Fittig synthesis and reduction; such reduction is a general feature of this type of reaction, and was encountered in the similar cases described in Part IV.

Di(naphthalene-2 : 7-dimethylene) (III) is a fourteen-membered ring compound with two rigid groups of seven atoms, in which considerable strain must be present owing to the close proximity of the two pairs of interior α-CH groups. The necessary separation of these groups to a carbon–carbon distance of something over 3 A. is probably achieved by distortion of the normal bond angles; the problem is precisely similar to that presented by di-*m*-xylylene discussed in the previous paper.

Direct dehydrogenation of (III) was unsuccessfully attempted in an inert atmosphere with sulphur, selenium, palladium–charcoal, and palladium black; the last two were also employed in inert solvents. After treatment with palladium black in an evacuated sealed tube at 300° for twenty-four hours a trace of the yellow coronene was isolated by hand-sorting, and identified spectroscopically by the presence of strong absorption bands at 3025 and 3400 A. When the reaction was continued for seven days and the product was fractionally sublimed and then crystallised from benzene, a fraction of a milligram of pure coronene was isolated and characterised by the identity of its *X*-ray powder photograph with that of an authentic specimen.

In view of the unsatisfactory nature of these direct dehydrogenations we investigated the action of aluminium chloride on (III) in boiling carbon disulphide, and found that it gave in high yield a mixture of 1 : 2-dihydrocoronene and a much smaller quantity of coronene. When the crude, mixed product was treated with palladium black at 260°, the dehydrogenated material isolated by sublimation in a vacuum and purified by passing its solution in benzene through a short column of alumina it gave finally pure coronene (VI) in 49% yield, calculated on the amount of (III) used. The coronene was identified by elementary analysis, *X*-ray powder photography, ultra-violet absorption spectroscopy, melting point, and formation of its picrate. In another experiment an attempt was made to separate the constituents of the mixture obtained from the aluminium chloride reaction, by processes involving sublimation, picrate formation, crystallisation, and hand-sorting. Two distinct crystalline materials were isolated in 40% and 0·34% yield respectively. The first, crystallising in compact, cubic crystals, formed a deep purple picrate (coronene picrate is bright red), and gave analytical figures corresponding to a dihydrocoronene. It was thought that this compound would be most probably 1 : 2-dihydrocoronene because of its method of preparation and because, of the five possible dihydrocoronenes (1 : 2-, 1 : 3-, 1 : 6-, 1 : 7-, 2 : 5-), the 1 : 2-compound has the greatest degree of aromatic character. This was confirmed by comparison of the ultra-violet absorption spectrum of the supposed 1 : 2-dihydrocoronene with that of 1 : 12-benzperylene (VII) (Clar, *Ber.*, 1932, **65**, 849) which differs from 1 : 2-dihydrocoronene only in the absence of the ethylene bridge. However, although the curves were almost identical for wave-lengths between 225 and 310 mμ., they differed appreciably between 310 and 400 mμ., and comparison with the absorption curve for coronene made it evident that there was not less than 15% of coronene present in the dihydro-compound, probably as a mixed crystal. Insufficient material was available to allow further separation of the constituents. The minor constituent of the reaction product of (III) with aluminium chloride crystallised in needles, and gave analytical figures close to those of coronene, and the ultra-violet absorption spectrum showed that it was probably mainly coronene with a certain amount of 1 : 2-dihydrocoronene, doubtless again in the form of a mixed crystal. We are greatly indebted to Mr. R. C. Seymour of the Department of Inorganic and Physical Chemistry of this University, and to Dr. E. Clar of the Department of Chemistry, The University, Glasgow, for advice in connection with the interpretation of the ultra-violet absorption curves. This minor constituent gave an *X*-ray powder photograph scarcely distinguishable from that of coronene, and it yielded coronene, isolated as its picrate, when dehydrogenated in presence of palladium black. Under these conditions the major product of the aluminium chloride reaction gave pure coronene (identified by an *X*-ray powder photograph) in 87% yield.

The use of aluminium chloride for bringing about cyclodehydrogenation to polycyclic aromatic hydrocarbons is well known. The process employed in this paper was suggested

mainly by the work of Ruzicka and Hösli (*Helv. Chim. Acta*, **1934**, **17**, 471) and of Buu-Hoï (*J. Org. Chem.*, **1949**, **14**, 1031).

The present method gives coronene in a four-step (virtually a three-step) synthesis from 2 : 7-dimethylnaphthalene in a yield of 4%; the overall yield from *p*-toluidine, the starting point for the synthesis of 2 : 7-dimethylnaphthalene, is about 0·8%. This synthesis has advantages over those previously described, and the yield could doubtless be improved by closer study. The first preparation of coronene, due to Scholl and Meyer (*Ber.*, **1932**, **65**, 902), proceeded in ten steps from the chloride of anthraquinone-1 : 5-dicarboxylic acid; the yield from this intermediate was not recorded but was undoubtedly extremely small. The second, due to Newman (*J. Amer. Chem. Soc.*, **1940**, **62**, 1683), required six steps from 7-methyltetralone and gave a 1·7% yield from this ketone; the latter was itself prepared in a four (virtually three)-step synthesis from toluene in probably about 50—60% yield, making the overall yield of coronene of the order of 1%. A disadvantage of the Newman synthesis is that the final step proceeds in only 5·5% yield.

When this work was nearly complete it was found that Wood and Stansfield (*J. Amer. Chem. Soc.*, **1942**, **64**, 2343) had proposed to prepare coronene from 2 : 7-dithioformylnaphthalene by reaction with copper to give the diolefinic analogue of (III), and then to convert this into coronene by cyclodehydrogenation. They were, however, unable to prepare 2 : 7-dithioformylnaphthalene, and for steric reasons it seems most unlikely that the diolefin corresponding to (III) could exist.

Experimental.

M. p.s, except those over 350°, are uncorrected. Microanalyses are by Mr. W. M. Eno, Bristol, and Drs. Weiler and Strauss, Oxford.

2 : 7-*Bisbromomethylnaphthalene* (II).—A mixture of 2 : 7-dimethylnaphthalene (I) (20·0 g., 1 mol.), *N*-bromosuccinimide (52·0 g., *ca.* 2·2 mols.; freshly prepared by the method of Lecocq, *Ann. Chim.*, 1948, **3**, 62), and benzoyl peroxide (0·3 g.) in dry carbon tetrachloride (150 c.c.), was boiled under reflux for 4½ hours, then cooled, and the solid containing the 2 : 7-*bisbromomethylnaphthalene* which is almost insoluble in cold carbon tetrachloride was collected and washed with cold carbon tetrachloride. The product was next ground with carbon tetrachloride, collected again, and washed with the same solvent. This material (40 g.) was extracted with boiling benzene (200 c.c.), the mixture filtered hot from undissolved succinimide (m. p. and mixed m. p. 123—124°), and the filtrate diluted with more benzene, extracted with 5% aqueous sodium hydroxide to remove the remaining succinimide, and finally washed, dried, and concentrated to a small bulk. The 2 : 7-bisbromomethylnaphthalene (19·8 g., 49%) separated slowly as elongated, hexagonal plates, m. p. 146—147° (Found, in material twice crystallised from benzene: C, 45·8; H, 3·3; Br, 50·9. $C_{12}H_{10}Br_2$ requires C, 45·9; H, 3·2; Br, 50·9%). The carbon tetrachloride-soluble product (30·5 g.) had m. p. 70—112°, and consisted of a difficultly separable mixture containing 2-bromomethyl-7-methylnaphthalene [m. p. 100° (decomp.); Buu-Hoï and Lecocq, *J.*, 1946, 830] and a tribromo-2 : 7-dimethylnaphthalene of unproved structure, probably 1-*bromo*-2 : 7-*bisbromomethylnaphthalene*. In another experiment in which less pure *N*-bromosuccinimide was used the latter compound was isolated by repeated crystallisation from benzene–light petroleum as needles (2·5 g.), m. p. 113—114° (Found: C, 37·3; H, 2·2; Br, 60·0. $C_{12}H_8Br_2$ requires C, 36·7; H, 2·4; Br, 61·0%).

The 2 : 7-bisbromomethylnaphthalene (1·0 g.) was converted into the related *bisthiuronium bromide* by boiling it with ethanol (100 c.c.) and thiourea (0·49 g.) for 2·5 hours, concentration (to *ca.* 50 c.c.), and addition of benzene. The solid was collected, washed (yield, 1·3 g.), and crystallised from ethanol, giving colourless prisms, m. p. 241° (decomp.), which may not be quite pure (Found, in material dried for 2 hours at 65°: C, 36·5; H, 4·0; N, 11·2; S, 14·3; Br, 31·5. $C_{10}H_6[CH_2{\cdot}S{\cdot}C(:NH){\cdot}NH_2,HBr]_2$ requires C, 36·0; H, 3·9; N, 12·0; S, 13·7; Br, 34·4%).

Reaction of 2 : 7-*Bisbromomethylnaphthalene with Sodium. Formation of* 1 : 2-*Di*-(7-*methyl*-2-*naphthyl*)-*ethane* (IV) *and Di*(*naphthalene*-2 : 7-*dimethylene*) (III).—2 : 7-Bisbromomethylnaphthalene (II) (6·5 g.) in purified dioxan (125 c.c.) was heated under reflux with sodium (2·0 g.) and sodium iodide (0·05 g.) for 24 hours, the mixture being shaken vigorously during the initial stages of the reaction in order to disperse the sodium. The cooled mixture was filtered, and the solid washed with warm dioxan (100 c.c.) (the solid insoluble in dioxan was freed from excess of sodium and inorganic salts by cautious addition to aqueous ethanol, collected, and dried, leaving polymeric material, 1·26 g.). The united dioxan filtrate and washings were evaporated under diminished pressure and the resulting pale pink solid was sublimed (*ca.* 0·1 mm.) at a temperature slowly rising to 220° (metal-bath). The colourless sublimate (1·60 g.) was again sublimed, and the following fractions were separately collected at the temperatures and during the times recorded: (1) 0·19 g., m. p. 80—88°; 100°, 3 hours; (2) 0·12 g., m. p. 122—123°; 135°, 1½ hours; (3) 0·16 g., m. p. 130—160°; 150°, ½ hour; (4) 0·31 g., m. p. >180°; 160°, 2 hours; (5) 0·63 g., m. p. up to 230°; 200°, 4 hours; (6) 0·04 g., m. p. 200—250°; 220°, 2 hours. The sublimate fractions (4) and (5) were united and dissolved in benzene, and the solution was allowed to cool very slowly so that large well-developed crystals were formed. The crystals were of two distinct types which, after being collected and dried, were separated by hand-sorting. The compound present in smaller quantity crystallised in thin, flat, nacreous plates, which after recrystallisation from benzene had m. p. 214—215° [Found: C, 92·6; H, 7·1%; *M* (Rast), 329. $C_{24}H_{22}$ requires C, 92·85; H, 7·15%; *M*, 310]; this substance is 1 : 2-*di*-(7-*methyl*-2-*naphthyl*)*ethane* (IV). The other component of the mixture, present in larger quantity, formed thick, clear, hexagonal plates (3—5-mm. sides), which after crystallisation from benzene had m. p. 237—238° [Found: C, 93·5; H, 6·8%; *M* (Rast), 288. $C_{24}H_{20}$ requires C,

93·5; H, 6·5%; *M*, 308]; this substance is *di(naphthalene-2 : 7-dimethylene)* (III). Repeated concentration of the benzene mother-liquors yielded further quantities of both compounds which were hand-separated, and each was then crystallised individually from benzene, giving finally as the total yields 1 : 2-di-(7-methyl-2-naphthyl)ethane, 0·14 g., and di(naphthalene-2 : 7-dimethylene), 0·53 g. Of the remaining fractions of the second sublimation process (1) was mainly 2 : 7-dimethylnaphthalene, (2) and (3) contained considerable amounts of bromine-containing material, and (6) was neglected.

The *picrate* of (III) was prepared from the hydrocarbon (14 mg.) and picric acid (20 mg.) in benzene (2 c.c.); it separated in ruby-red prisms, m. p. 180—181° (Found : N, 8·0. $C_{24}H_{20}.C_6H_3O_7N_3$ requires N, 7·8%).

Preparation of Coronene (VI) *by Cyclodehydrogenation of Di(naphthalene-2 : 7-dimethylene)* (III) *with Aluminium Chloride followed by Dehydrogenation with Palladium.*—Di(naphthalene-2 : 7-dimethylene) (III) (0·16 g.) was boiled under reflux for 23 hours with carbon disulphide (25 c.c.) and finely powdered aluminium chloride (0·75 g.). The solution became green and deposited a deep green solid, which was finally treated with ice and dilute hydrochloric acid and extracted with chloroform, and the organic layer was washed with water, dried ($MgSO_4$), and evaporated, leaving a yellow-brown solid which was intimately mixed with palladium black (0·4 g.) and heated at 260° for 4·5 hours in an atmosphere of carbon dioxide in a sublimation apparatus with a cold finger. The organic material was finally sublimed on to the cold finger by careful heating with a free flame at *ca.* 0·1 mm. pressure. The yellow sublimate was dissolved in boiling benzene, the solution filtered from a small amount of palladium, and by next morning the crude coronene had separated as rather dark, yellow-brown needles (0·102 g.). This product was passed in benzene (200 c.c.) through a short alumina column which did not retain the coronene but removed a strongly adsorbed dark impurity; evaporation of the solvent and final recrystallisation from benzene gave pure coronene as amber-yellow needles (5—15 mm. long) (0·077 g., 49%) (Found : C, 95·6; H, 4·1. Calc. for $C_{24}H_{12}$: C, 96·0; H, 4·0%). This coronene gave m. p. 442°, determined in a sealed tube in an electrically heated apparatus, the temperature being recorded by means of a calibrated thermocouple. It was finally identified by the complete correspondence of all the lines in its *X*-ray powder photograph with those given by an authentic specimen of coronene.

The picrate was prepared in benzene solution, and separated as bright red needles which decomposed between 310° and 325° (Found : C, 67·8; H, 2·9; N, 7·8. Calc. for $C_{24}H_{12}.C_6H_3O_7N_3$: C, 68·1; H, 2·9; N, 7·9%).

Reaction of Di(naphthalene-2 : 7-dimethylene) (III) *with Aluminium Chloride.* 1 : 2-*Dihydrocoronene.*—Di(naphthalene-2 : 7-dimethylene) (0·30 g.) was treated with aluminium chloride (1·4 g.) in carbon disulphide (40 c.c.), and the product isolated by extraction with chloroform as previously described. This product was passed in benzene through a column of alumina which retained dark material, and the eluate was distilled, leaving a yellow-brown powder (0·23 g.) which showed a yellow-green fluorescence in ultra-violet light but could not be satisfactorily crystallised. It was therefore sublimed at 0·1 mm. at the temperatures given below, the following fractions being collected : (1) yellow, partly crystalline material, 35 mg., 150°, 2 hours; (2) yellow crystalline material, 185 mg., 190—250° during 4 hours. The second fraction (185 mg.) was treated in benzene solution with a solution of picric acid in benzene and a little light petroleum added; after several hours the purple needles were collected and dissolved in benzene, and the picrates decomposed by passage through a short column of alumina which was finally eluted with hot benzene. The yellow eluate was evaporated, and the residue crystallised from benzene, giving, first, long yellow needles, and then compact yellow, almost cubic crystals. This mixture was collected, dried, and separated as far as possible by hand-picking, and each product separately recrystallised from benzene, a few more of the almost cubic crystals being obtained from the recrystallisation of the needle form.

The 1 : 2-*dihydrocoronene* (V) (now known to be contaminated with coronene; see Introduction) which forms the yellow, cubic crystals was obtained in a total yield of 114 mg. It is more soluble in benzene than the needles, and the solution shows a strong blue fluorescence even in daylight, being thereby distinguished from that of coronene. The m.p., determined as for coronene (above), was 365—367° (Found : C, 95·3; H, 4·8. $C_{24}H_{14}$ requires C, 95·3; H, 4·7%). The *picrate* prepared in benzene solution formed deep purple needles which decomposed between 330° and 370° (Found : C, 67·8; H, 3·4; N, 7·6. $C_{24}H_{14}.C_6H_3O_7N_3$ requires C, 67·8; H, 3·2; N, 7·9%).

The material which formed the needle-shaped crystals was obtained in a yield of 10 mg. only. After further crystallisation from benzene–light petroleum (b. p. 60—80°) it had m. p. 418° (Found : C, 95·6; H, 4·6%). It showed a blue fluorescence in ultra-violet light, and the picrate formed short, reddish-purple needles from benzene.

Dehydrogenation of these two products was effected with palladium. The cubic 1 : 2-dihydrocoronene (30 mg.) was mixed with palladium black (200 mg.) and heated in an atmosphere of carbon dioxide for 5 hours at 200—255° in a sublimation apparatus. The volatile material was now transferred to the cold finger by careful heating with a free flame at 0·1 mm., collected, and crystallised from benzene. Coronene separated as long yellow needles, m. p. 442° (26 mg., 87%), and was identified by an *X*-ray powder photograph. The derived picrate was indistinguishable from coronene picrate.

A similar experiment starting from the needles (2 mg.) yielded red needles of a picrate which were indistinguishable from those of coronene picrate.

The authors' thanks, in addition to those already recorded, are also due to the Department of Scientific and Industrial Research for a maintenance allowance (to F. G.), and to Dr. H. F. Kay and Mr. P. C. Bailey of the H. H. Wills Physical Laboratory of this University for the *X*-ray powder photographs.

THE UNIVERSITY, BRISTOL. [*Received, January 25th*, 1951.]

244. *The Synthesis of Sugars from Simpler Substances. Part I. The* in vitro *Synthesis of the Pentoses.*

By L. Hough and J. K. N. Jones.

Aldopentose sugars have been synthesised from formaldehyde, from glycollic aldehyde and glyceraldehyde, and from dihydroxyacetone and glycollic aldehyde. The origin of the pentose sugars in Nature is discussed.

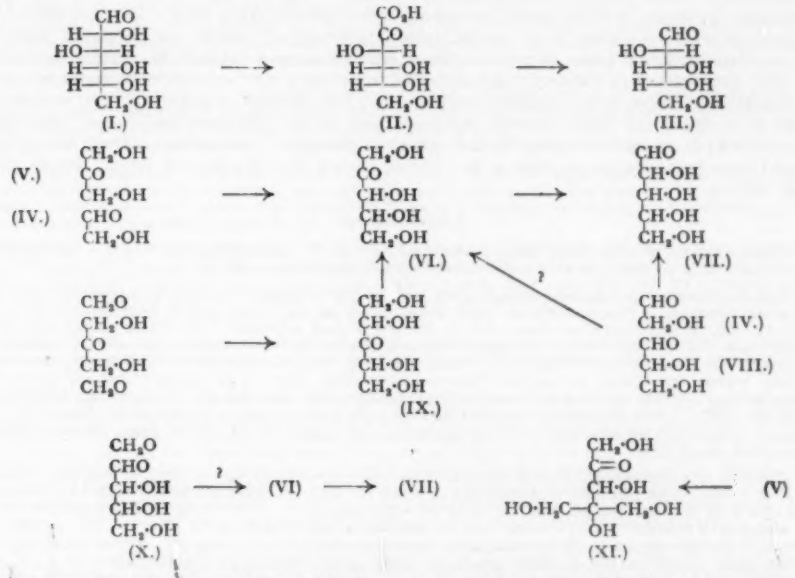
The biogenetical origin of the monosaccharides has long been the subject of scientific enquiry and, although it has been established that the hexoses can arise from the condensation of the two trioses, glyceraldehyde and dihydroxyacetone, as their phosphate derivatives, under the influence of enzymes, yet the origin of the pentose sugars remains obscure. The pentoses occur abundantly in plants, usually in combination in the form of a pentosan as, for example, in araban or xylan, or in combination with other sugars such as in the plant gums and mucilages. The frequent association of the pentoses with hexuronic acids and hexoses, such as the occurrence of araban, pectic acid, and galactan in pectic substances, has led to the suggestion that they are derived from hexoses by a process involving oxidation of the primary alcoholic group on $C_{(6)}$ of the hexose, yielding a hexuronic acid, subsequent decarboxylation of which affords a pentose. By this process, D-galactose would yield L-arabinose, and D-glucose would afford D-xylose, and it is precisely these hexose and pentose sugars which are associated one with another in plant materials. On the other hand, the isolation of D-mannuronic acid, and the failure to detect D-lyxose in plant products, has thrown some doubt on this hypothesis (see Hirst, *J.*, 1949, 522, for a detailed discussion of these problems).

It has also been suggested that the pentose sugars may arise from the 2-ketohexonic acids, *e.g.*, (II) ⟶ (III), again by decarboxylation. This suggestion receives support from the synthesis of D-arabinose (III) *in vitro*, from D-gluconic acid by use of Fenton's reagent (*J.*, 1899, **75**, 577), and of D-arabinose and D-ribose *in vivo* from D-glucose (I) *via* 2-keto-D-gluconic acid (II) (Dickens and Glock, *Nature*, 1950, **166**, 33; Cohen and Scott, *Science*, 1950, **111**, 543). D-Arabinose and D-ribose have been encountered as constituents of both plant and bacterial materials (Léger, *Compt. rend.*, 1912, **155**, 173; Corley, *J. Biol. Chem.*, 1929, **82**, 269). The absence of L-glucose, L-fructose, and L-mannose (all of which could yield L-arabinose) and of D-gulose and D-idose (the parent sugars from which D-xylose would be formed) in plant materials suggests that L-arabinose and D-xylose are not formed by this simple mechanism. On the other hand, the D-xylose might arise from glucose by a mechanism similar to the formation of D-ribose from this hexose.

The possibility remains that the pentoses are synthesised in a similar manner to the hexoses in the plant by aldol-type condensation of small fragments. Earlier work (Orthner and Gerisch, *Biochem. Z.*, 1933, **259**, 30) showed that glycollic aldehyde (IV) and dihydroxyacetone (V) combined in alkaline solution to form a mixture of reducing sugars, which, it was suggested, were mainly ketopentoses (VI) and from which an osazone with the characteristics of a pentosazone was isolated; Euler and Euler (*Ber.*, 1906, **39**, 45) detected arabinose amongst the condensation products of formaldehyde (cf. Karrer and Krauss, *Helv. Chim. Acta*, 1931, **14**, 820). Pentose sugars (VII) may also be envisaged as arising from the condensation of D- or L-glyceraldehyde (VIII) and glycollic aldehyde (IV), from dihydroxyacetone and two mols. of formaldehyde (XIV) and subsequent isomerisation of the ketose (IX), or from a tetrose (X) and formaldehyde.

We have examined the mixture of sugars produced on condensation of dihydroxyacetone and glycollic aldehyde in alkaline solution. The products were separated on the paper chromatogram and, by their rate of movement and by the colours produced on reaction with a variety of specific spray reagents (Hough, Jones, and Wadman, *J.*, 1950, 1702), all four pentose sugars were detected, arabinose and xylose predominating. The mixture of sugars was fractionated on a column of cellulose by partition chromatography, butanol–water being used as the mobile phase (Hough, Jones, and Wadman, *J.*, 1949, 2511). After separation, the fractions were shown to contain severally ribose, lyxose, xylose, and arabinose by paper chromatography. Efforts to crystallise these sugars directly were unsuccessful, but crystalline derivatives of DL-xylose and DL-arabinose were isolated, namely, DL-xylose toluene-*p*-sulphonylhydrazone and DL-arabinose benzoylhydrazone. After hydrolysis of the latter in the presence of benzaldehyde, crystalline DL-arabinose was obtained. Similarly, hydrolysis of the DL-xylose derivative afforded DL-xylose, a syrup. Since DL-arabinose may be resolved through its menthyl-

phenylhydrazone (Neuberg, *Ber.*, 1905, **38**, 868), and as glycollic aldehyde and dihydroxyacetone have been synthesised from bromoacetaldehyde and nitromethane, respectively (Piloty, *Ber.*, 1897, **30**, 3161), this constitutes a complete synthesis of D- and L-arabinose. The crystalline DL-derivatives were identical with authentic specimens prepared from D + L-xylose and D + L-arabinose respectively and, in each case, they possessed higher melting points than the corresponding D- or L-derivative. We are greatly indebted to Dr. T. Malkin for confirming the identity of these crystalline derivatives by *X*-ray analysis. The evidence indicated that ribose and lyxose were present in small quantity, but crystalline derivatives were not obtained.



D-Glyceraldehyde and glycollic aldehyde, on reaction in alkaline solution, gave a mixture of optically active sugars containing all four pentoses, xylose and arabinose again predominating. During this reaction some epimerisation of the D-glyceraldehyde to L-glyceraldehyde and dihydroxyacetone occurs, and consequently crystals of DL-xylose toluene-*p*-sulphonylhydrazone, D + DL-arabinose benzoylhydrazone and D + DL-sorbose were isolated and not the pure D-isomers. DL-Sorbose arises from the conversion of some of the D-glyceraldehyde into DL-glyceraldehyde and dihydroxyacetone and their subsequent condensation (cf. Fischer and Baer, *Helv. Chim. Acta*, 1936, **19**, 519).

One mode of condensation of dihydroxyacetone with formaldehyde might be envisaged as involving one molecule of ketose with two molecules of aldehyde with the formation of a symmetrical ketose (IX), with subsequent rearrangement first to a ketopentose (VI) and then to an aldopentose (VII). Aldopentoses were not detected as a result of this reaction at room temperature but, when the reaction mixture is heated in alkaline solution, aldopentoses are produced. This formation of pentose sugars may, however, result from the conversion of the formaldehyde into glycollic aldehyde and subsequent synthesis of the pentose sugars.

Utkin (*Chem. Abstr.*, 1950, **44**, 3910*a*) has isolated a ketohexose homologue of apiose termed dendroketose (XI) from the polymerisation of two molecules of dihydroxyacetone. We have observed that dihydroxyacetone alone in alkali gave a high yield of a ketose sugar which moves at the same rate as xylose on the paper chromatogram, butanol–ethanol–water being used as the mobile phase. Consequently, in reactions involving glyceraldehyde and dihydroxyacetone, the xylose fraction is likely to be contaminated with this sugar. Dendroketose gives a bright yellow colour with *p*-anisidine hydrochloride.

The polymerisation of formaldehyde in alkaline solution yields a complex mixture of sugars

("formose") in which pentose sugars can be detected. The syrup obtained from the polymerisation of paraformaldehyde with lime water was separated by partition chromatography on a column of cellulose, propanol–water being the mobile phase. A fraction rich in pentose sugars was collected and refractionated on a column of cellulose, with butanol–water as the mobile phase. This gave a portion of sugars which contained mainly xylose with small quantities of arabinose and ketose sugars. By utilising the fact that, when butanol–water is used as the mobile phase on the paper chromatogram xylose occupies a position between arabinose and lyxose, whereas when the phenol–water solvent system is employed, xylose moves more slowly and is completely separated from the other pentose sugars, a method for the separation of xylose from the other sugars is available. Accordingly, the mixture of sugars was separated on sheets of filter-paper, the phenol–water solvent being used. The majority of the impurities were separated from the DL-xylose, sufficient of which was extracted from the appropriate section of paper to give its characteristic toluene-*p*-sulphonylhydrazone derivative.

The preparation *in vitro* of pentose sugars from one-, two-, or three-carbon fragments by polymerisation under mild conditions suggests that the pentoses, D-xylose and L-arabinose, are formed in the plant from glycollic aldehyde and either dihydroxyacetone or, less likely, glyceraldehyde as such, or possibly through their phosphate derivatives. Their biosynthesis would then be analogous to that of the hexose sugars (cf. Hough and Jones, *Nature*, 1951, **167**, 180).

Experimental.

(Optical rotations were observed in aqueous solution at 20° unless otherwise stated. All R_G values quoted are those observed in *n*-butanol–ethanol–water mixture at *ca.* 20°.)

Unless otherwise stated, the products from each of the following reactions were separated on three separate sheet-paper chromatograms, using respectively as the mobile phase butanol–ethanol–water (40 : 11 : 19), butanol–pyridine–water (10 : 3 : 3), and phenol saturated with water containing 1% of acetic acid. After separation, the paper chromatograms were dried, sprayed with a solution of *p*-anisidine hydrochloride in butanol, and heated. In this manner, the four pentoses, namely, arabinose, xylose, lyxose, and ribose, are readily discerned, since they show up as characteristic red spots on a white background, the position of the spots being characteristic of each sugar (cf. Partridge, *Biochem. J.*, 1948, **42**, 238). Other chromatograms were sprayed with resorcinol–phosphoric acid mixture in aqueous ethanol, with which the ketohexoses give characteristic red colours (cf. Hirst and Jones, *Discuss. Faraday Soc.*, 1949, No. 7, 271)].

Reaction of D-*Glyceraldehyde with Glycollic Aldehyde.*—D-Glyceraldehyde (3·0 g.) (Baer and Fischer, *J. Biol. Chem.*, 1939, **128**, 463) was dissolved in water (10 c.c.), and glycollic aldehyde (2·0 g.) (prepared from 5·5 g. of dihydroxymaleic acid) in water (50 c.c.) was added. The solution was adjusted to pH 11 by addition of 0·3N-barium hydroxide, and the alkaline solution made up to 100 c.c. The quantity of barium hydroxide required to bring the solution to the required pH depends on the purity of the dihydroxymaleic acid, which usually contains traces of oxalic acid resulting in the formation of a colloidal precipitate of barium oxalate on the addition of the barium hydroxide. For this reason, it was not possible to follow any change in optical rotation of the solution. A portion of the yellow solution was withdrawn each day and examined on the paper chromatogram. After 10 days at 20° in a stoppered vessel, no further change was seen in the complex mixture of pentose and other sugars observable on the chromatogram. Sulphuric acid (2N.) was then added to the reaction mixture until no more barium sulphate was precipitated. The precipitate was removed by filtration, and the filtrate passed down a column of anion-exchange resin (Amberlite IR4B). The neutral solution was then concentrated under reduced pressure at 40° to an orange syrup (3·1 g.), which was separated on a column of cellulose, *n*-butanol half-saturated with water being used as eluent. Portions of the effluent were examined on the paper chromatogram, and the fractions so divided that, as far as possible, separation of the pentose sugars was achieved. Solvents were removed under reduced pressure yielding: fraction I (0·127 g.), $[\alpha]_D^{20}$ −6°; fraction II (0·091 g.), $[\alpha]_D$ −4°; fraction III (0·186 g.), $[\alpha]_D$ −2°; fraction IV (0·153 g.), $[\alpha]$ −22°; fraction V (0·145 g.); fraction VI (0·207 g.); fraction VII (0·315 g.); and residue, (0·290 g.). The total yield was 1·514 g. Examination of these fractions on the paper chromatogram showed that each consisted of two or more components and that fractions I—V inclusive contained aldopentoses. These fractions also contained ketohexoses since they gave, after separation on the paper chromatogram, characteristic red spots on spraying with resorcinol–phosphoric acid solution and heating; the positions of these spots corresponded with those of the four ketohexoses.

Fractions I and II contained pentose sugars, which moved to the same position as ribose (R_G 0·21) and lyxose (R_G 0·19) respectively on the paper chromatogram, gave a characteristic red colour with *p*-anisidine hydrochloride, and yielded furfuraldehyde on distillation with hydrochloric acid. Since no crystalline derivatives were isolated, this evidence is only presumptive and does not conclusively identity the sugars as ribose and lyxose.

Fraction III contained two pentose sugars, one of which was conclusively identified as xylose (R_G 0·17), and the other, present in small amount, showed properties identical with those of lyxose on the chromatogram. A portion of the syrup (90 mg.) was heated on the boiling-water bath with a solution of toluene-*p*-sulphonylhydrazine (90 mg.) in methanol (5 c.c.) for 30 minutes. The solution was then concentrated to *ca.* 2 c.c. and cooled and, after storage, the crystals (15 mg.) of DL-*xylose toluene*-p-

sulphonylhydrazone were collected on the filter, washed with methanol, and dried; they had m. p. 154° (decomp.) and $[\alpha]_D$ 0° ± 5° (*c*, 4·0 in pyridine) (Found: C, 45·2; H, 6·0; N, 8·8. $C_{12}H_{16}O_4N_2S$ requires C, 45·3; H, 5·7; N, 8·7%). This fraction therefore contains at least 15 mg. of DL-xylose.

An *X*-ray powder photograph of these crystals showed that they differed from an authentic specimen of D-xylose toluene-*p*-sulphonylhydrazone, m. p. 147° (decomp.), $[\alpha]_D$ −32° (*c*, 4·3 in pyridine), but were identical with DL-xylose toluene-*p*-sulphonylhydrazone, m. p. 154° (decomp.), prepared by dissolving equimolecular quantities of the corresponding hydrazones of D- and L-xylose in methanol and crystallising. [The L-xylose was prepared from D-sorbitol by oxidation with hydrogen peroxide in the presence of ferrous sulphate (Fenton's reagent)—details will be published later.] The DL-xylose derivative is more insoluble in methanol than the D-isomer.

Fraction IV contained only one pentose sugar, namely, arabinose. A portion of the syrup (0·07 g.) was heated on a boiling-water bath with benzoylhydrazine (0·05 g.) in alcohol (2 c.c.) for 1 hour. On concentration, the benzoylhydrazone (12 mg.), m. p. 194—195° (not depressed on admixture with DL-arabinose benzoylhydrazone) separated. This material showed $[\alpha]_D$ −25° [*c*, 3·6 (calc. on arabinose) in 2N-sulphuric acid] and evidently consisted of the D- and the DL-isomer. An *X*-ray powder photograph of the recrystallised material gave a picture identical with that of authentic DL-arabinose benzoylhydrazone, m. p. 194—195°; no D-isomer could be detected. All attempts to crystallise fraction IV by nucleation with D- and with DL-arabinose were unsuccessful. DL-Arabinose, prepared by recrystallisaton of equimolecular amounts of the D- and the L-sugar, has m. p. 163—164° (Wohl, *Ber.*, 1893, **26**, 742, gives m. p. 163·5—164·5° for this sugar). This fraction therefore contains at least 15 mg. of D + DL-arabinose.

Fraction V contained a low concentration of arabinose. A ketose sugar, which moved to the same position as fructose on the chromatogram and gave a red colour with the resorcinol spray, was also present. Glucosazone of characteristic crystalline shape was obtained on heating a portion of the syrup with a solution of phenylhydrazine acetate.

Fraction VI crystallised on storage. The crystals were separated after trituration with methanol and, after recrystallisation from this solvent, had m. p. 161—162° (mixed m. p. with L-sorbose, 161—162°). They were identified as D + DL-sorbose. The crystals gave a positive test for a ketose sugar and, with a variety of solvents, moved at the same rate as sorbose on the chromatogram, and had $[\alpha]_D$ +10° (*c*, 0·572) (D-sorbose has $[\alpha]_D$ +43·4°).

Fraction VI contained sugars which moved on the paper chromatogram at the same rate as galactose and gave colour reactions characteristic of aldohexoses; no derivative of this sugar, however, could be isolated.

Reaction of Dihydroxyacetone with Glycollic Aldehyde.—Dihydroxyacetone (0·9 g.) and glycollic aldehyde (0·6 g., from 1·48 g. of dihydroxymaleic acid) were dissolved in water (40 c.c.), and sufficient barium hydroxide (0·3N.) was added to bring the solution to pH 11. The solution was kept at this pH for 14 days. Barium ions were then precipitated by addition of 2N-sulphuric acid, and the filtered solution passed through a column of Amberlite IR4B resin to remove acids. The filtrate was concentrated under reduced pressure to a syrup (1·378 g.) which contained all four pentose sugars as well as other carbohydrate material. The syrup was fractionated on a column of cellulose, *n*-butanol half saturated with water being used as the mobile phase, and yielded the following fractions.

Fraction I (0·220 g.) contained a pentose sugar which moved at the same rate as ribose on the chromatogram; ketopentose sugars may also have been present; no crystalline derivative was isolated. Fraction II (0·092 g.) contained two pentose sugars, identified by their rate of movement on the chromatogram as ribose and xylose; lyxose may also have been present; ketose sugars were also detected; no crystalline derivative was isolated. Fraction III (0·050 g.) contained a small amount of xylose; the major component was an unknown sugar (dendroketose?), which moved to the same position on the chromatogram as did an authentic specimen of dendroketose and with *p*-anisidine hydrochloride gave a similar colour reaction.

Fraction IV (0·221 g.) contained the pentose, xylose, and the same unknown sugar (dendroketose?). A portion of this syrup (38 mg.) when heated with toluene-*p*-sulphonylhydrazine (40 mg.) in methanol gave DL-xylose toluene-*p*-sulphonylhydrazone (25 mg.), m. p. and mixed m. p. 154° (decomp.), the identity of which was confirmed by *X*-ray analysis. A little of the hydrazone was dissolved in warm 2N-hydrochloric acid, and a portion of the solution placed on the paper chromatogram. An authentic D-xylose derivative treated in this manner gave D-xylose which moved at the same rate and gave the same colour reactions as the sugar from the DL-xylose derivative. The toluene-*p*-sulphonylhydrazone derivative (110 mg. from 150 mg. of Fraction IV) was converted into the sugar by warming it for 1 hour with benzaldehyde (0·5 c.c.) dissolved in aqueous methanol (10 c.c.) containing one drop of acetic acid. The cooled solution was exhaustively extracted with ether, and the aqueous solution evaporated to a syrup of DL-xylose (48 mg.) which did not crystallise. Efforts to crystallise authentic DL-xylose were fruitless.* Fischer and Ruff (*Ber.*, 1900, **33**, 2145) give m. p. 129—131° for DL-xylose. Fraction IV contains at least 74 mg. of DL-xylose.

Fraction V (0·050 g.) contained ketohexose sugars, xylose, and arabinose. Fraction VI (0·211 g.) consisted of ketohexose sugars and arabinose. A portion of the syrup (100 mg.) was heated under reflux with a solution of benzoylhydrazine (100 mg.) in methanol (2 c.c.). On concentration of the solution, crystals of DL-arabinose benzoylhydrazone (40 mg.), m. p. and mixed m. p. 194°, separated. An *X*-ray powder photograph of the crystals was identical with that of an authentic specimen of DL-arabinose benzoylhydrazone. Conversion into the parent sugar was achieved by dissolving the derivative in a little 2N-hydrochloric acid. The resultant sugar moved at the same rate and gave the same colour

* *Added in Proof.*—This material has now been obtained crystalline.

reaction on the chromatogram as did L-arabinose. The benzoylhydrazone, m. p. 194° (40 mg. isolated from a second preparation of pentose sugars), was warmed with benzaldehyde (200 mg.), water (2 c.c.), glacial acetic acid (1 drop), and sufficient methanol to give complete dissolution. After 24 hours, the solution was diluted with water, and extracted with ether, and the aqueous solution then evaporated to a syrup, which crystallised. The DL-arabinose (8 mg.) was recrystallised from methanol; m. p. and mixed m. p. 163°. Fraction VI contained at least 44 mg. of DL-arabinose.

Preparation of Formose: Isolation of DL-*Xylose as its Toluene*-p-*sulphonylhydrazone.*—Paraformaldehyde (10 g.) was suspended in water (200 c.c.), and calcium hydroxide (2 g.) added. The solution was heated on the boiling-water bath for 45 minutes. During this time the paraformaldehyde dissolved, and the solution, initially colourless, became yellow; the odour of formaldehyde disappeared and was replaced by that of caramel. Karrer and Krauss (*loc. cit.*) found *ca.* 0·4% of pentose sugars to be present in a sample of formose prepared by a similar procedure. An examination of a portion of the reaction mixture on the paper chromatogram showed the presence of a complex mixture of ketohexose, aldohexose, and pentose sugars. The solution was cooled, and a solution of oxalic acid added to remove calcium salts, which were filtered off. The filtrate was passed down a column of Amberlite IR4B resin to remove acidic material, and the neutral solution concentrated to a syrup (8 g.) which was fractionated by chromatography on a column of cellulose, *iso*propyl alcohol and water (19 : 1) being used as the mobile phase. In this manner, a fraction (1·42 g.) containing all the four pentose sugars was obtained. This material was then further fractionated on a column of cellulose, butanol half saturated with water being the eluent. By this procedure, a fraction (0·600 g.) rich in xylose and containing a little arabinose (?) and ribose (?) was obtained. This fraction still contained sugars other than pentoses, since separation into three fraction on the paper chromatogram could be achieved by using phenol–water as mobile phase. Accordingly, a portion (0·4 g.) of the syrup was refractionated by separation on two sheets of Whatman No. 1 filter-paper (24″ × 18″), phenol–water being used as mobile phase. After separation, the paper was dried, and the appropriate section of filter-paper holding xylose was extracted (Flood, Hirst, and Jones, *J.*, 1948, 1679) with methanol (Soxhlet). The syrup (94 mg.) which remained on evaporation of the solvent did not crystallise. It was first extracted with ether to remove phenolic impurities and the insoluble residue was then boiled with a solution of toluene-*p*-sulphonylhydrazine (20 mg.) in methanol, and the solution evaporated to a small volume, whereupon DL-xylose toluene-*p*-sulphonylhydrazone (20 mg.), m. p. 154° (decomp.), separated. The product, recrystallised from methanol, had m. p. and mixed m. p. 154° (decomp.), and was identical with an authentic specimen in that on solution in dilute hydrochloric acid, it gave xylose which moved on the chromatogram at the same rate as an authentic specimen of sugar prepared from D-xylose toluene-*p*-sulphonylhydrazone.*

Condensation of Dihydroxyacetone and Paraformaldehyde.—Dihydroxyacetone (0·9 g.) and paraformaldehyde (0·9 g.) were dissolved in water (20 c.c.), and barium hydroxide (0·3N.; 1 c.c.) added. At intervals, portions of the solution were withdrawn; no pentose sugars could be detected even after 3 months. After this or the original solution was heated on the boiling-water bath for 30 minutes, the presence of pentose and other sugars could be detected on the paper chromatogram. When a portion of the solution was boiled with hydrochloric acid furfuraldehyde was formed.

Condensation of Glycollic Aldehyde and Paraformaldehyde.—Glycollic aldehyde (*ca.* 1·1 g.) in water (30 c.c.) and paraformaldehyde (0·6 g.) were mixed and the solution was adjusted to pH 11 by addition of 0·3N-barium hydroxide. After 6 days the pattern of sugar on the chromatogram was constant. The major component was an unknown sugar which gave an intense yellow colour with the *p*-anisidine spray and moved at the same rate as xylose in butanol–ethanol–water, and displayed the properties similar to those of dendroketose prepared from dihydroxyacetone (Utkin, *loc. cit.*). Small quantities of pentose sugars (mainly xylose) were also detected on the chromatogram.

We thank Drs. J. F. W. McOmie and W. D. Ollis for their helpful criticism.

THE UNIVERSITY, BRISTOL. [*Received, December 15th*, 1950.]

* *Added in Proof.*—We have since isolated DL-arabinose from formose in the following manner. The formose preparation was heated under reflux with methanolic hydrogen chloride (1%) and, after removal of the acid, the resulting glycosides were separated on a column of cellulose, butanol–water being used as the mobile phase. The faster-moving methylpentosides were separated and hydrolysed, and the reducing sugars refractionated on the column. This gave a fraction rich in arabinose, which, on reaction with benzhydrazide, gave DL-arabinose benzoylhydrazone, m. p. 194°, from which DL-arabinose was obtained.

245. *The Adsorption Isotherm of Langmuir and of Brunauer, Emmett, and Teller for Multilayers where* n *is* 2.

By D. C. Jones and E. W. Birks.

An analysis of the adsorption isotherm of Langmuir and of Brunauer, Emmett, and Teller (B.E.T.) for multilayers where the number of such layers is limited to two is made. The *realisable* isotherms show interesting changes of type as σ_1/σ_2 or c reaches certain critical values, σ_1 and σ_2 being the relative lives of adsorbed molecules in the first and second layers respectively: the B.E.T. assumption, that $\sigma_2 = \sigma_{\text{liquid}}$, need not be made in this case. For $c = 4$ the isotherm is a rectangular hyperbola, passing through the origin and therefore, for this case, bilayer adsorption on this model gives an isotherm of the same form as that given by the Langmuir monolayer equation. Deviations from the hyperbola occur as $c \gtrless 4$ and the deviations are simply related to the value of c.

One of the authors has pointed out (Jones *et al.*, *J.*, 1951, 126) the resemblances existing between the Brunauer–Emmett–Teller equations for multilayer adsorption and those of Langmuir (*J. Amer. Chem. Soc.*, 1918, **40**, 1361) for Cases IV and VI, which are concerned, respectively, with adsorption where n molecules can occupy one elementary space and where multilayers, in limited numbers up to n, or where n is infinite, can occur.

Equation 1 is essentially that of Langmuir for Case IV where η is the total quantity of adsorbed gas expressed in g.-mols., N is Avogadro's number, N_0 is the number of elementary spaces per sq. cm., μ is the collision number, and $\sigma_1, \sigma_2 \ldots\ldots \sigma_n$ are the relative lives of the adsorbed molecules in the elementary spaces containing 1—n molecules.

$$\frac{N}{N_0}\eta = \frac{\sigma_1\mu + 2\sigma_1\sigma_2\mu^2 + 3\sigma_1\sigma_2\sigma_3\mu^3 + \ldots\ldots\ldots}{1 + \sigma_1\mu + \sigma_1\sigma_2\mu^2 + \sigma_1\sigma_2\sigma_3\mu^3 + \ldots\ldots} \quad \ldots\ldots (1)$$

If now the Langmuir assumption is made that $\sigma_1 \neq \sigma_2$ but that $\sigma_3 = \sigma_3 = \sigma_4$, etc., then equation 1 becomes:

$$\frac{N}{N_0}\eta = \frac{\sigma_1\mu[1 + 2(\sigma_2\mu) + 3(\sigma_2\mu)^2 + \ldots. n(\sigma_2\mu)^{n-1}]}{1 + \sigma_1\mu[1 + (\sigma_2\mu) + (\sigma_2\mu)^2 + \ldots (\sigma_2\mu)^{n-1}]} \quad \ldots\ldots (2)$$

The corresponding equation given by Brunauer ("The Adsorption of Gases and Vapours," Oxford Univ. Press, 1945) is

$$\frac{V}{V_m} = \frac{cx}{1-x} \cdot \frac{1 - (n+1)x^n + nx^{n+1}}{1 + (c-1)x - cx^{n+1}} \quad \ldots\ldots\ldots\ldots (3)$$

$$= \frac{cx}{1-x} \cdot \frac{(1-x)^2(1 + 2x + 3x^2 + \ldots\ldots nx^{n-1})}{(1-x)[1 + cx\,(1 + x + x^2 + \ldots x^{n-1})]} \quad \ldots\ldots (4)$$

$$= \frac{cx(1 + 2x + 3x^2 + \ldots\ldots nx^{n-1})}{1 + cx\,(1 + x + x^2 + \ldots\ldots x^{n-1})} \quad \ldots\ldots\ldots (5)$$

Comparing equations 2 and 5 it is seen that they are identical if $\sigma_1\mu = cx$, and $\sigma_2\mu = x$: the quantity $c = \sigma_1/\sigma_2$, the ratio of the relative lives of the adsorbate on the first and on the subsequent layers (*vide* Jones, *loc. cit.*).

Consideration of the case for $n = 3$ and the general case will be dealt with in further papers. In this communication the case for $n = 2$ is analysed. This has especial interest because (1) it has been reported to occur experimentally; (2) no assumptions need be made as to the value assigned to σ_2 (in the B.E.T. theory $\sigma_2 = \sigma_L$ where σ_L is the relative life of the adsorbed molecule on the liquid surface): so that this objection to the B.E.T. theory is not present in this case; (3) the analysis would also apply to the case where a monolayer is not exceeded but where *two* molecules can be present per elementary space.

Using the B.E.T. nomenclature but remembering that c is now σ_1/σ_2 and has not the special significance allotted to it by these authors, we have, from equation 5:

$$\frac{V}{V_m} = \frac{cx(1+2x)}{1+cx+cx^2} \quad \ldots\ldots\ldots\ldots \quad (6)$$

$$\frac{1}{c}\cdot\frac{\mathrm{d}(V/V_m)}{\mathrm{d}x} = \frac{1+4x+cx^2}{(1+cx+cx^2)^2} \quad \ldots\ldots\ldots\ldots \quad (7)$$

$$\frac{1}{c}\cdot\frac{\mathrm{d}^2(V/V_m)}{\mathrm{d}x^2} = \frac{2[(2-c)-3cx-6cx^2-c^2x^3]}{(1+cx+cx^2)^3} \quad \ldots\ldots \quad (8)$$

The conclusions that will be drawn as regards the main features of the isotherm are illustrated in Figs. 1 *A*, *B*, and *C*, these sections of the figure referring to the cases $c > 4$, $c = 4$, and $c < 4$ respectively.

Equation 6 gives $V/V_m = 0$ if $x = 0$; $V/V_m = 0$ also for $x = -1/2$ except where $c = 4$. All the isotherms therefore pass through the origin and through the point ($V/V_m = 0$, $x = -1/2$) with this exception. In the case of $c = 4$ equation 6 becomes $V/V_m = 4x/(1+2x)$, which is a rectangular hyperbola with asymptotes $V/V_m = 2$ and $x = -1/2$ (Fig. 1 *B*).

FIG. 1 *A*.

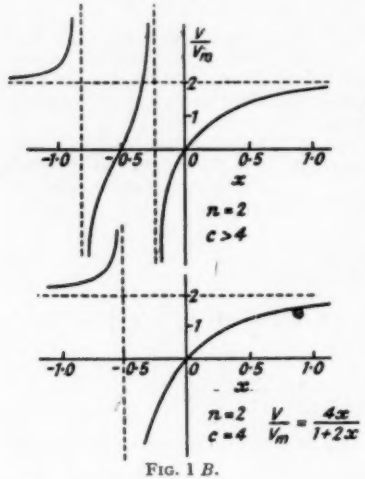


FIG. 1 *C*.

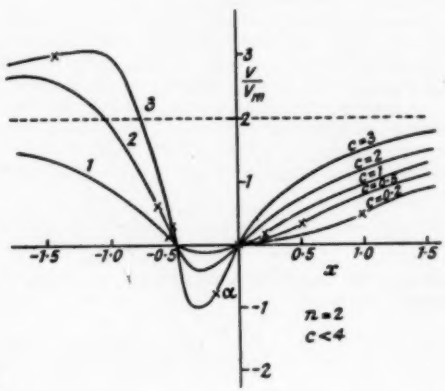


FIG. 1 *B*.

$V/V_m = \infty$ if $cx^2 + cx + 1 = 0$: it is readily seen that if $c > 4$ there are two real negative roots to this equation, *i.e.*, there are *two* asymptotes for negative values of x; these asymptotes approach each other as c diminishes; when $c = 4$ the asymptotes coincide at $x = -1/2$ (two equal roots) (Fig. 1 *B*) if $0 < c < 4$ the roots are imaginary.

Again, V/V_m approaches 2 as x approaches infinity; indeed, as can be deduced from equation 5, in general, V/V_m approaches n asymptotically as x approaches infinity; this of course also applies to the well-known Case 1 of Langmuir where $n = 1$.

From equation 7 it can be shown that there are no turning values if x is positive, or, if x is negative, when $c > 4$ (Fig. 1 *A*); there are two turning points if $c < 4$, at negative values of x, the curves having a maximum and a minimum, but only one asymptote, $V/V_m = 2$ (Fig. 1 *C*). When $c = 4$

$$\frac{\mathrm{d}(V/V_m)}{\mathrm{d}x} = \frac{c}{1+4x+4x^2} = \frac{c}{(1+2x)^2} = \infty \text{ if } x = -\tfrac{1}{2}.$$

The gradient is thus ∞ at $x = -1/2$ and has finite values if x is $>$ or $<$ $-1/2$ (Fig. 1 *B*).

The slope at the origin for all isotherms is c.

The roots of the cubic equation comprising the numerator of equation 8 have been determined by the cosine method and confirm that when $4 > c > 2$ there are three *negative* points of inflection; when $c = 2$ there are two negative points of inflection and *one* at the origin;

when $c < 2$ two points of inflection are negative and the third is now positive; when c has the values 1, 0·5, and 0·2, the corresponding positive points of inflection are, approximately, at the values of $x = 0{\cdot}22$, 0·5, and 1, respectively. The points of inflection on the curves shown are marked by crosses in Fig. 1 *C*. The negative point of inflection marked α in Fig. 1 *C* near the minimum of the curve for $c = 3$, moves to the origin when $c = 2$, and then occurs at higher positive values of x as the value of c diminishes.

It will be noticed that the numerator of equation 8 contains a term independent of x, *viz.*, $(2 - c)$. Further analysis has shown that this constant term is present whatever the value of n $(n > 1)$; it is characteristic of this Langmuir multilayer model. It follows that when $c = 2$ there is always a point of inflection at the origin and this means that a change of adsorption type occurs always at this value of c in this model. This type change is heralded by corresponding changes in the shapes of the isotherms. This can be seen clearly from the realisable isotherms shown in Fig. 2, and the corresponding $x/(V/V_m)$ against x plots given in Fig. 3.

FIG. 2.

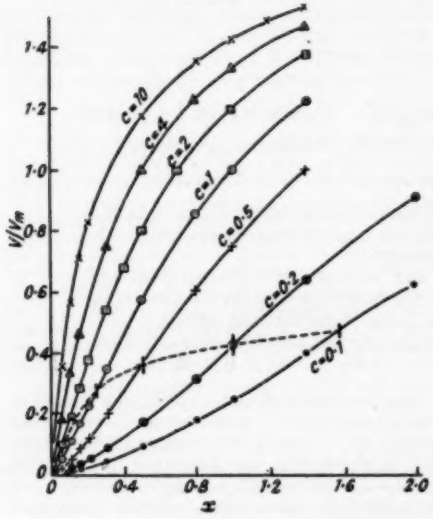
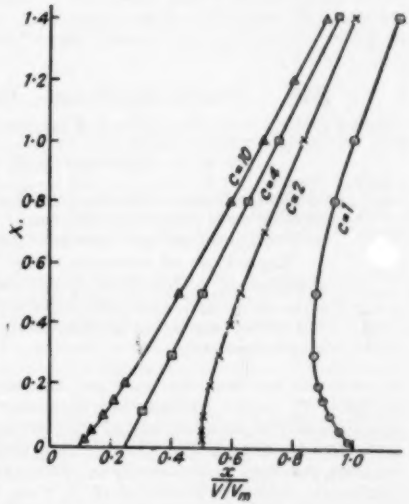


FIG. 3.



For $c = 4$ the isotherm is a rectangular hyperbola passing through the origin; this equation is of the same character as that for Langmuir's Case 1, and, as seen in Fig. 3, a straight line is obtained in this case.

If $c > 4$ there are deviations from the linear relation, *e.g.*, $c = 10$ in Fig. 3, and, if $c < 4$ much greater deviations, but now in the opposite direction, *e.g.*, $c = 1$ and 2 in Fig. 3. The corresponding changes in the shapes of the isotherms can be seen in Fig. 2; the almost linear portion for $c = 2$ found occurring from the origin to values of $x = 0{\cdot}3$ (approx.) and even to higher values of x for $c = 1$, is due to the position of the point of inflection whose locus is indicated by a broken line in the diagram. These linear portions give slopes approximately equal to the initial slope c. It may be noticed that although for this case of $n = 2$, only when $c = 4$ would the curve give a true straight line plot as in Fig. 3, yet deviations would not be large for neighbouring values of c, and further, even in the range from $c = 10$ to $c = 1$, extrapolation of the plot at low values of x to $x = 0$ would give fairly accurately the value of $1/c$ (see Fig. 3). Thus from equation 6

$$\frac{x}{V/V_m} = \frac{1}{c} \cdot \frac{1 + cx + cx^2}{1 + 2x} \quad \ldots\ldots\ldots\ldots \quad (9)$$

$$= \frac{1 + 2x}{4} + \frac{\frac{4}{c} - 1}{4(1 + 2x)} \quad \ldots\ldots\ldots\ldots \quad (10)$$

From equation 9 it is seen that the function $x/(V/V_m) = 1/c$ when $x = 0$. The transformation in equation 10 gives the deviation of the function from the case of $c = 4$ (the hyperbola); the first term on the right-hand side of equation 10 is the value of the function for $c = 4$, and the second term gives the deviations, which are negative or positive as $c >$ or < 4: further, when c is large the numerator of the second term approaches the value -1 and the deviations approach a constant value for each value of x; also the deviation becomes greater for a given value of c as x approaches 0. These points have illustrations in Fig. 3 and may be useful in the interpretation of experimental results.

In this case then, the *realisable* adsorption curves are of type I if $c > 2$ (interpreting type I as the isotherm which is always concave downwards and not necessarily obeying the Langmuir Case 1 equation); type V if $0{\cdot}2$ (approx.) $< c < 2$. If $0 < c < 0{\cdot}2$ (approx.), the positive point of inflection is at values of $x > 1$ and the adsorption type could perhaps best be called VA, although it resembles type III in being convex downwards for the whole of the *realisable* curve.

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246. *Anodic Syntheses. Part IV. Synthesis of (+)- and (−)-Tuberculostearic Acids.*

By R. P. LINSTEAD, J. C. LUNT, and B. C. L. WEEDON.

Optically active intermediates have been employed in the anodic synthesis of fatty acids previously described. In this manner the pure enantiomorphs of tuberculostearic acid have been prepared.

Electrolyses of mixtures of (+)- and (−)-(methyl hydrogen β-methylglutarate) (I) with octanoic acid led to (+)- and (−)-3-methylundecanoic acids (II). (+)- and (−)-Tuberculostearic acids were similarly obtained from mixtures of methyl hydrogen azelate with (−)- and (+)-3-methylundecanoic acid respectively.

RECENTLY it has been demonstrated that the enantiomorphs of methyl hydrogen β-methylglutarate (I), unlike optically active α-alkyl acids, undergo the Kolbe electrolytic reaction without racemisation of the asymmetric centres (Part III, *J.*, 1950, 3333; Ställberg-Stenhagen, *Arkiv Kemi*, 1950, **2**, 95). It therefore seemed probable that the unsymmetrical coupling reactions, resulting from electrolyses of mixtures of a monocarboxylic acid and a half-ester of a dicarboxylic acid (cf. Parts I and II, *J.*, 1950, 3326, 3331), would furnish a valuable synthesis of pure optical isomers of branched-chain fatty acids, provided that neither component possessed an asymmetric centre in the position α to the carboxyl group. This has now been shown to be the case by substituting the enantiomorphs of (I) for the (±)-half ester in the synthesis of (±)-tuberculostearic acid (III) previously reported (Part II).

Electrolyses in methanol of mixtures of octanoic acid (2 mols.) with (+)- and (−)-(methyl hydrogen β-methylglutarate) (I) (1 mol.), and subsequent hydrolysis of the crude products, gave (+)- and (−)-3-methylundecanoic acids (II) in 48% yields (based on half-esters). Similar electrolyses of mixtures of the (+)- and the (−)-form of (II) (1 mol.) with methyl hydrogen

$$\begin{array}{l} \mathrm{Me{\cdot}[CH_2]_6{\cdot}CO_2H} + \mathrm{HO_2C{\cdot}CH_2{\cdot}CHMe{\cdot}CH_2{\cdot}CO_2Me} \\ \qquad\qquad\qquad\qquad\qquad\qquad\quad \text{(I.)} \\ \qquad\qquad\qquad\quad \downarrow \\ \mathrm{Me{\cdot}[CH_2]_7{\cdot}CHMe{\cdot}CH_2{\cdot}CO_2H} + \mathrm{HO_2C{\cdot}[CH_2]_7{\cdot}CO_2Me} \\ \text{(II.)} \qquad\qquad\qquad\quad \downarrow \\ \qquad\qquad\qquad\quad \mathrm{Me{\cdot}[CH_2]_7{\cdot}CHMe{\cdot}[CH_2]_8{\cdot}CO_2H} \quad \text{(III.)} \end{array}$$

azelate (2 mols.) led to the isolation of slightly impure specimens of (−)- and (+)-10-methyloctadecanoic (tuberculostearic) acids (III) respectively in 30% yields (based on II). Purification was readily effected by regeneration of the (−)-acid from the amide and by low-temperature crystallisation of the (+)-acid. On admixture of equal amounts of the two enantiomorphs (±)-tuberculostearic acid was obtained.

The optical rotations of the branched-chain fatty acids described in this paper are in excellent agreement with those reported by previous authors (see Table).

Acid.	Optical rotation.* Cason *et al.*[1]	Ställberg-Stenhagen.[2]	Present authors.
(+)-3-Methylundecanoic acid	α_D^{25} +4·45°	α_D^{25} +4·50°	α_D^{23} +4·50°
(−)- ,, ,, ...	α_D^{25} −4·47°	α_D^{25} −4·53°	α_D^{18} −4·52°
(+)-10-Methyloctadecanoic acid	α_D^{26} +0·08°	α_D^{25} +0·09° ± 0·02°	α_D^{18} +0·07° ± 0·02°
(−)- ,, ,, ...	α_D^{26} −0·045°	α_D^{25} −0·11° ± 0·02°	α_D^{19} −0·08° ± 0·02°

* Homogeneous, 1-dm. cell. [1] Prout, Cason, and Ingersoll, *J. Amer. Chem. Soc.*, 1948, **70**, 298. [2] Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1948, **26**, *A*, No. 12.

While this work was in progress, Ställberg-Stenhagen (1950, *loc. cit.*) described the synthesis of optically active β-methyl-carboxylic acids by electrolysis of equimolar mixtures of fatty acids with enantiomorphs of (I). More recently the same author (1950, *loc. cit.*, p. 431) has prepared (−)-3(*L*) : 6(*D*)-dimethyltetracosanoic acid * by electrolysis of a mixture of stearic acid and (−)-[methyl hydrogen 3(*L*) : 6(*D*)-dimethylsuberate]. The yields (based on optically active intermediates) given by the Swedish worker for these unsymmetrical coupling reactions are somewhat lower than those which were obtained in the present investigation by using an excess of the optically inactive components.

Experimental.

Yields in unsymmetrical-coupling reactions are calculated on the optically active starting material. Commercial absolute methanol was used as a solvent in all electrolyses without purification. The optical rotations of the branched-chain fatty acids are given in the Table.

(+)-L-*and* (−)-D-(*Methyl Hydrogen β-Methylglutarate*).—The resolution of (±)-(methyl hydrogen β-methylglutarate) was effected in batches of *ca.* 30 g. essentially as described previously (Linstead, Lunt, and Weedon, *J.*, 1950, 3333). By carrying out the successive crystallisations of each batch of product from the mother-liquors obtained in the corresponding crystallisation of the preceding batch, the overall yields of the (+)- and (−)-half-esters were raised to 48%.

(+)-D-3-*Methylundecanoic Acid* (cf. preparation of the inactive acid, *idem, ibid.*, p. 3331).—A mixture of (+)-*L*-(methyl hydrogen β-methylglutarate) (10·0 g., 0·0625 mol.) and octanoic acid (18·0 g., 0·125 mol.; prepared as described in Part I, *J.*, 1950, 3326) was added to sodium methoxide (from sodium, 0·09 g., 0·0039 mol.) in methanol (75—80 c.c.). The resulting solution was electrolysed in the usual manner, using two platinum plates (4 × 2·5 cm.), placed *ca.* 1·5 mm. apart, as electrodes and a current of 2 amps.

The preceding experiment was repeated, and the cell contents from the two electrolyses were combined, neutralised by the addition of a few drops of acetic acid, and evaporated under reduced pressure. The residue was hydrolysed with aqueous-methanolic potassium hydroxide, and the products were separated into neutral and acidic fractions. Distillation of the non-saponifiable fraction gave *n*-tetradecane (12·0 g., 49%), b. p. 128°/19 mm., n_D^{21} 1·4275. Distillation of the acidic fraction yielded (+)-*D*-3-methylundecanoic acid (11·9 g., 48%), b. p. 117°/0·5 mm., n_D^{26} 1·4350 (Ställberg-Stenhagen, *Arkiv Kemi, Min., Geol.*, 1948, **26**, *A*, No. 12, gives b. p. 99—101°/0·2 mm.). The amide crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 86·5—86·7° [*idem, loc. cit.*, gives m. p. 87·2—87·7° (corr.)]. The residue (2·72 g.), m. p. 81·5—82·5°, from the distillation of the acidic fraction was crystallised from benzene–light petroleum (b. p. 60—80°) and finally from water containing a small amount of methanol, giving β(*D*) : β′(*D*)-dimethylsuberic acid (2·03 g.), m. p. 83—83·5° (Linstead, Lunt, and Weedon, *ibid.*, p. 3333, give m. p. 83·5°).

(−)-L-3-*Methylundecanoic Acid*.—Repetition of the preceding preparation after substituting (−)-*D*-(methyl hydrogen β-methylglutarate) (9·3 g.) for the (+)-half-ester in each of the electrolyses gave : (i) *n*-Tetradecane (12·2 g., 49%). (ii) (−)-*L*-3-Methylundecanoic acid (11·2 g., 48%), b. p. 114—117°/0·4 mm., $n_D^{18\cdot5}$ 1·4401. The amide crystallised from light petroleum (b. p. 40—60°) in needles, m. p. 86·3—86·7° [Ställberg-Stenhagen, 1948, *loc. cit.*, gives m. p. 87·2—87·7° (corr.)]. (iii) β(*L*) : β′(*L*)-Dimethylsuberic acid (1·57 g.), m. p. 83·2—83·5° (Linstead, Lunt, and Weedon, *loc. cit.*, give m. p. 83·5—83·7°).

(−)-D-10-*Methyloctadecanoic Acid* (*Tuberculostearic Acid*) (cf. preparation of the inactive acid, *idem, ibid.*, p. 3331). A mixture of (+)-*D*-3-methylundecanoic acid (5 g., 0·025 mol.) and methyl hydrogen azelate (9 g., 0·045 mol.) was added to a solution of sodium methoxide (from sodium, 0·03 g., 0·0014 mol.) in methanol (25—30 c.c.). The solution thus obtained was electrolysed in the usual manner using two platinum plates (2·5 × 2·5 cm.), placed 1·5 mm. apart, as electrodes and a current of 1·2 amps.

The preceding experiment was repeated, and the products from the two electrolyses were combined, and worked up in the manner described above for *D*-3-methylundecanoic acid.

Distillation of the non-saponifiable fraction gave (−)-9(L) : 12(D)-*dimethyleicosane* (1·25 g., 16%), b. p. 113—116°/0·5 mm., n_D^{26} 1·4421, α_D^{22} −0·94° (homogeneous, *l* = 1) (Found : C, 85·0; H, 14·9. $C_{22}H_{46}$ requires C, 85·05; H, 14·95%).

A solution of the acidic fraction in ether (*ca.* 65 c.c.) was cooled to 0° and the solid (2·55 g.), m. p. 119—121°, which separated was removed by filtration and recrystallised from methanol yielding thapsic

* See note on nomenclature in Part III, *J.*, 1950, 3333.

acid (tetradecane-1 : 14-dicarboxylic acid) (2·14 g.) as plates, m. p. 123—124° (Carmichael, *J.*, 1922, **121**, 2545, gives m. p. 124°). The ethereal mother-liquors were evaporated, the residual thapsic acid was removed as the lead salt (2·13 g.), and the monocarboxylic acids distilled giving (i) an unsaturated liquid (1·75 g.), b. p. 75—130°/0·2 mm. and (ii) crude (−)-*D*-10-methyloctadecanoic acid (4·64 g., 31%), b. p. 160—162°/0·2 mm., n_D^{23} 1·4501, m. p. 8—11°. The crude tuberculostearic acid (4·28 g.) was converted into the amide (by Ställberg-Stenhagen's method, 1948, *loc. cit.*). After two crystallisations from ether and one from acetone, this was obtained as plates (2·52 g., 54%), m. p. 75·7—76·2° [*idem, loc. cit.*, gives m. p 76·4—76·6° (corr.)]. Hydrolysis of the amide gave the pure acid (1·82 g., 82% based on amide), b. p. 180° (bath-temp.)/0·1 mm., m. p. 12·5—12·9° [*idem, loc. cit.*, gives b. p. 175—178°/0·7 mm., m. p. 12·4—12·8° (corr.)] (Found : C, 76·6; H, 12·55. Calc. for $C_{19}H_{38}O_2$: C, 76·45; H, 12·85%).

(+)-L-10-*Methyloctadecanoic Acid.*—Repetition of the preceding experiment with the use of (−)-*L*-3-methylundecanoic acid instead of the (+)-acid gave : (i) (+)-9(D) : 12(L)-*dimethyleicosane* (1·27 g., 16%), b. p. 122°/0·6 mm., $n_D^{19\cdot5}$ 1·4445, a_D^{16} +0·92° (homogeneous, $l = 1$) (Found : C, 84·95; H, 14·8. $C_{22}H_{46}$ requires C, 85·05; H, 14·95%); (ii) thapsic acid (2·52 g.), m. p. 123—124°; (iii) lead thapsate (1·9 g.); (iv) an unsaturated acidic liquid (2·0 g.), b. p. 72—145°/0·1 mm.; and (v) crude (+)-*L*-10-methyloctadecanoic acid (4·42 g., 30%), b. p. 160—162°/0·1 mm., n_D^{26} 1·4508, m. p. 10·5—12·0°, which after one recrystallisation from acetone at *ca.* −20° yielded the pure acid as prisms (2·2 g.), m. p. 12·3—12·8° [*idem, loc. cit.*, gives m. p. 12·5—12·8° (corr.)] (Found : C, 76·7; H, 12·65. Calc. for $C_{19}H_{38}O_2$: C, 76·45; H, 12·85%).

Investigation of the Unsaturated Acidic Fractions from the Preparation of (−)- *and* (+)-*Tuberculostearic Acids.*—The unsaturated materials were redistilled and the fractions with b. p. 125—127°/16 mm. (1·0 g.) and 72—75°/0·2 mm. (1·0 g.) were combined. Redistillation gave a mixture of octanoic and octenoic acids (1·1 g.), b. p. 123—124°/13 mm., n_D^{22} 1·4350 (Found : hydrogen number, 251. Calc. for octenoic acid, $C_8H_{14}O_2$: hydrogen number, 142).

A solution of the mixed acids (1·0 g.) in ethyl acetate (15 c.c.) was shaken in hydrogen in the presence of palladium–calcium carbonate catalyst (0·6 g.; 3% of Pd) until absorption was complete. After removal of catalyst and solvent, the residue was distilled giving slightly impure octanoic acid (0·8 g.), b. p. 140° (bath-temp.)/15 mm., m. p. 11—15·5°, n_D^{21} 1·4274 (Greaves *et al.*, *J.*, 1950, 3326, give f. p. 15·5—15·3°, n_D^{27} 1·4251). The *p*-bromophenacyl ester had m. p. 65·5—66° undepressed on admixture with a specimen, m. p. 65·5—66°, prepared from authentic octanoic acid.

(±)-10-*Methyloctadecanoic Acid.*—On admixture of equal amounts of the two enantiomorphs described above and crystallisation of the mixture from acetone at −15°, the racemic acid was obtained as prisms, m. p. 20·9—21·2°. The solid obtained on rapid cooling of the molten acid had m. p. 24·1—24·4°. On slow cooling of the molten acid, another form, m. p. 25·8—26·4°, was obtained (Ställberg-Stenhagen, 1948, *loc. cit.*, gives m. p. 20·9—21·6° and 25·8—26·1°; Linstead, Lunt, and Weedon, *J.*, 1950, 3331, give m. p. 21·0—21·4° and 24·1—24·5°).

One of us (J. C. L.) thanks the Department of Scientific and Industrial Research for a Maintenance Grant.

Imperial College of Science and Technology,
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247. 4 : 5-iso*Propylidene* 1 : 2-3 : 6-*Dianhydromannitol.*

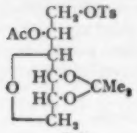
By A. B. Foster and W. G. Overend.

A new dianhydro-derivative of mannitol has been characterised, namely, 4 : 5-*iso*propylidene 1 : 2-3 : 6-dianhydromannitol. The ethylene oxide ring in this compound undergoes scission on treatment with water, hydrobromic acid, lithium aluminium hydride, methylmagnesium iodide, sodium methoxide, or methanolic ammonia, with the exclusive formation of $C_{(1)}$-substituted derivatives.

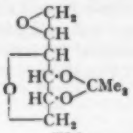
Dianhydro-derivatives of mannitol incorporating two butylene oxide rings (*e.g.*, 1 : 4-3 : 6-dianhydromannitol) or two ethylene oxide rings (*e.g.*, 1 : 2-5 : 6-dianhydromannitol) have been examined in considerable detail (Wiggins, *J.*, 1945, 4; 1946, 384). This paper describes some derivatives of a new dianhydromannitol containing a butylene oxide and an ethylene oxide anhydro-ring, namely, 1 : 2-3 : 6-dianhydromannitol.

When 2-acetyl 4 : 5-*iso*propylidene 1-toluene-*p*-sulphonyl 3 : 6-anhydromannitol (I), obtained from 4 : 5-*iso*propylidene 3 : 6-anhydromannitol (Foster and Overend, *J.*, 1951, in the press) by partial reaction with toluene-*p*-sulphonyl chloride and subsequent acetylation, was treated with sodium methoxide, it was converted into 4 : 5-*iso*propylidene 1 : 2-3 : 6-dianhydromannitol (II), evidence for the structure of which may be summarised as follows. The location of the toluene-*p*-sulphonyloxy-group at $C_{(1)}$ was established by treating (I) with sodium iodide in acetone under standard conditions, 0·87 mole of sodium toluene-*p*-sulphonate being precipitated. Since all

the hydroxyl groups in (I), other than those at $C_{(1)}$ and $C_{(3)}$, are protected by groups resistant to alkali, the newly formed anhydro-ring must bridge $C_{(1)}$ to $C_{(3)}$. Since $C_{(1)}$ is not an asymmetric centre the dianhydro-derivative retains the mannitol configuration.

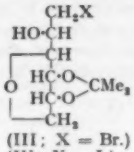


(I.)

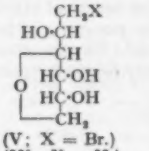


(II.)

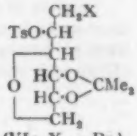
(Ts = *p*-$C_6H_4Me{\cdot}SO_2{\cdot}$)



(III; X = Br.)
(IV; X = I.)
(VII; X = H.)
(X; X = NH_2.)
(XI; X = OMe.)



(V; X = Br.)
(IX; X = H.)



(VI; X = Br.)
(VIII; X = H.)

In attempts to prepare 4 : 5-*iso*propylidene 1 : 2-3 : 6-dianhydromannitol (II) from 4 : 5-*iso*propylidene 1 : 2-ditoluene-*p*-sulphonyl 3 : 6-anhydromannitol by treatment with sodium methoxide, the starting material was recovered unchanged. A satisfactory explanation of this result has not yet been found and further experiments are in progress.

The well-known stability of butylene oxide anhydro-rings contrasts with the lability of their ethylene oxide analogues (see Peat, *Adv. Carbohydrate Chem.*, 1946, **2**, 37). The reactions of (II) which contains both types of anhydro-ring elegantly emphasise this difference. When 4 : 5-*iso*propylidene-1 : 2-3 : 6-dianhydromannitol (II) was boiled under reflux with acetone containing 0·14N-hydrobromic acid, 3 : 6-anhydro-1-bromo-1-deoxymannitol (V) and its 4 : 5-*iso*propylidene derivative (III) were obtained. The latter product resulted from the scission of the ethylene oxide ring by hydrobromic acid and was characterised as its 2-toluene-*p*-sulphonate (VI). Evidence for the location of the bromine atom at $C_{(1)}$ was obtained by catalytic hydrogenation, which eliminated the bromine atom and gave a syrupy deoxy-derivative (VII) [also characterised as its toluene-*p*-sulphonate (VIII)]. There was no reaction between (VIII) and sodium iodide in acetone under standard conditions, so that the toluene-*p*-sulphonyloxy-residue was located at $C_{(3)}$. Consequently, (VII) must have been 4 : 5-*iso*propylidene 3 : 6-anhydro-1-deoxymannitol, and (VIII) its 2-toluene-*p*-sulphonate. Since (III) was converted into (VII) by direct replacement of bromine by hydrogen it must have been 4 : 5-*iso*propylidene 3 : 6-anhydro-1-bromo-1-deoxymannitol. Since catalytic hydrogenation of (V) followed by introduction of *iso*propylidene and toluene-*p*-sulphonyl groups gave 4 : 5-*iso*propylidene 2-toluene-*p*-sulphonyl 3 : 6-anhydro-1-deoxymannitol (VIII) identical with that already described, its structure must be as stated, namely 3 : 6-anhydro-1-bromo-1-deoxymannitol. There was no evidence of the formation of 2-bromo-derivatives. Hydrolysis of (VII) with mineral acid gave syrupy 3 : 6-anhydro-1-deoxymannitol (IX).

The lability of the ethylene oxide ring in (II) is emphasised by the fact that it undergoes scission simply by boiling of its aqueous solution : the only product was 4 : 5-*iso*propylidene 3 : 6-anhydromannitol; no sorbitol derivative was detected.

In a similar manner, when (II) was treated with lithium aluminium hydride the only product isolated was 4 : 5-*iso*propylidene 3 : 6-anhydro-1-deoxymannitol (VII), characterised as its 2-toluene-*p*-sulphonate (VIII).

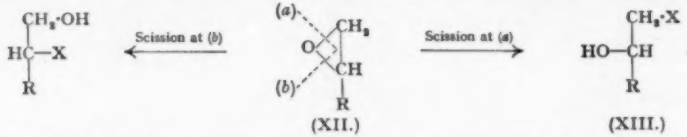
Grignard reagents have long been known to react with compounds containing ethylene oxide rings (Blaise, *Compt. rend.*, 1902, **134**, 557; Grignard, *ibid.*, 1903, **136**, 1260); for example, ethylene oxide and ethylmagnesium bromide give 2-bromoethanol. 4 : 5-*iso*Propylidene 1 : 2-3 : 6-dianhydromannitol (II) and methylmagnesium iodide in ether gave a crystalline compound containing iodine; catalytic hydrogenation of this substance, followed by reaction with toluene-*p*-sulphonyl chloride, gave 4 : 5-*iso*propylidene 2-toluene-*p*-sulphonyl 3 : 6-anhydro-1-deoxymannitol (VIII), indicating that the Grignard reaction gave 4 : 5-*iso*propylidene 3 : 6-anhydro-1-deoxy-1-iodomannitol (IV).

The reagents mentioned above, which are either acidic or neutral in character, exert no effect on the butylene oxide ring of (II), thereby demonstrating the difference in stability of the ethylene oxide and butylene oxide rings in this compound. The corresponding action of an alkaline reagent was shown by treatment of (II) with sodium methoxide. The syrupy compound isolated was designated as 1-methyl 4 : 5-*iso*propylidene 3 : 6-anhydromannitol (XI) since its crystalline toluene-*p*-sulphonate did not react with sodium iodide in acetone under standard conditions.

Treatment of (II) with methanolic ammonia at 120° afforded a syrupy amino-derivative, the

structure of which could not be conclusively proved but by analogy with other workers' results (Ohle *et al.*, *Ber.*, 1935, **68**, 2176; 1936, **69**, 1022, 1636; Wiggins, *J.*, 1946, 388) is provisionally designated as 4 : 5-*iso*propylidene 1-amino-3 : 6-anhydro-1-deoxymannitol (X).

Scission of non-terminal ethylene oxide rings by acidic, neutral, and alkaline reagents is well known, and may occur on either side of the ring-oxygen atom, affording a mixture of two isomeric products. On the other hand, however, the reaction of terminal ethylene oxide rings (XII) with similar reagents (generic formula, R'–X) leads to unidirectional scission of the ring



(XII.) (XIII.)

at (*a*) and products with the substituents in a terminal position (XIII). This is supported by the observations of numerous workers but a discordant note was struck by Swern, Billen, and Knight (*J. Amer. Chem. Soc.*, 1949, **71**, 1152) who claimed that the ethylene oxide ring in propylene oxide underwent scission on both sides of the ring oxygen when treated with allyl alcohol in the presence of an acid catalyst. The experiments outlined earlier are in opposition to this and support the postulate of unidirectional scission.

Experimental.

2-*Acetyl* 4 : 5-iso*Propylidene* 1-*Toluene*-p-*sulphonyl* 3 : 6-*Anhydromannitol*.—A solution of 4 : 5-*iso*propylidene-3 : 6-anhydromannitol (1·0 g.), prepared by Foster and Overend's method (*J.*, 1951, in the press), in dry pyridine (8 c.c.) was cooled to 0° and treated during 1 hour with toluene-*p*-sulphonyl chloride (1·0 mol., 0·95 g.). The mixture was kept at 0° for a further hour and then at room temperature overnight. Freshly distilled acetic anhydride (2 c.c.) was next added and the mixture set aside at room temperature for a further day. Dilution with water caused separation of the crystalline *product* which after recrystallisation from aqueous methanol was obtained as colourless needles (1·27 g.), m. p. 95—96°, $[\alpha]_D^{20}$ −23·2° (*c*, 0·52 in methanol) (Found: C, 53·9; H, 6·1. $C_{16}H_{24}O_8S$ requires C, 54·0; H, 6·0%).

Reaction of the Foregoing Derivative with Sodium Iodide in Acetone.—2-Acetyl 4 : 5-*iso*propylidene 1-toluene-*p*-sulphonyl 3 : 6-anhydromannitol (0·2 g.) and sodium iodide (1·5 mols., 0·112 g.) in dry acetone (10 c.c.) were heated in a sealed tube at 115—120° for 4 hours. The precipitated sodium toluene-*p*-sulphonate (85 mg.) which was collected in a sintered-glass funnel, washed with dry acetone, and dried at 130° for 30 minutes, corresponded to 87·6% of the amount for complete exchange of one toluene-*p*-sulphonyloxy-group.

Action of Sodium Methoxide on the Foregoing Toluene-p-*sulphonyl Derivative*.—A solution of 2-acetyl 4 : 5-*iso*propylidene 1-toluene-*p*-sulphonyl 3 : 6-anhydromannitol (1·11 g.) in chloroform (10 c.c.) was shaken vigorously with sodium methoxide (from sodium, 0·24 g., and methanol, 5 c.c.) at room temperature for 20 minutes. It was then diluted with chloroform (50 c.c.) and washed thrice with water. The dried ($MgSO_4$) chloroform solution was evaporated and the straw-coloured residue (0·56 g.) distilled. 4 : 5-iso*Propylidene* 1 : 2-3 : 6-*dianhydromannitol* (0·4 g.) was obtained as a colourless mobile liquid, b. p. 75—85° (bath-temp.)/0·01 mm., n^{21} 1·4558, $[\alpha]_D^{20}$ −64° (*c*, 0·53 in methanol). It crystallised on refrigeration but could not be satisfactorily recrystallised; it had m. p. 27—28° (Found: C, 57·1; H, 7·7. $C_9H_{14}O_4$ requires C, 58·0; H, 7·5%).

Non-reaction of Sodium Methoxide with 4 : 5-iso*Propylidene* 1 : 2-*Ditoluene*-p-*sulphonyl* 3 : 6-*Anhydromannitol*.—Under the conditions described by Richtmyer and Hudson (*J. Amer. Chem. Soc.*, 1941, **63**, 1730), 4 : 5-*iso*propylidene 1 : 2-ditoluene-*p*-sulphonyl 3 : 6-anhydromannitol (0·95 g.) (Foster and Overend, *loc. cit.*) was dissolved in chloroform (13 c.c.), cooled to 0°, and treated with a solution of sodium (0·2 g.) in dry methanol (5 c.c.) also cooled to 0°. The mixture was set aside at 0° for 3 days and then at room temperature for a further day. It was then diluted with chloroform (50 c.c.), washed thrice with water, dried ($MgSO_4$), and freed from solvent. The crystalline residue (0·9 g.) was recrystallised from ethanol, being obtained in colourless needles, m. p. 123—124° alone or on admixture with the starting material.

Action of Hydrobromic Acid on 4 : 5-iso*Propylidene* 1 : 2-3 : 6-*Dianhydromannitol*.—A solution of the dianhydro-compound (1·8 g.) in acetone–water (125 c.c.; 7 : 3) containing 2N-hydrobromic acid (7·5 c.c.) was boiled under reflux for 5 hours. The acid was neutralised by lead carbonate, and the insoluble lead residues were collected and washed with hot acetone. The filtrate was evaporated under diminished pressure until the acetone had been completely removed, and the remaining aqueous solution was thrice extracted with ether (total volume, 100 c.c.). Evaporation of the ethereal solution yielded a syrupy fraction A, and of the aqueous solution a syrupy fraction B.

Identification of Fraction A.—This fraction could not be crystallised. Distillation yielded a homogeneous, colourless, viscous liquid (1·39 g.), b. p. 115—120° (bath-temp.)/0·01 mm., which gave positive tests for halogen. It was 4 : 5-iso*propylidene* 3 : 6-*anhydro*-1-*bromo*-1-*deoxymannitol* and had n^{18} 1·4970 and $[\alpha]_D^{20}$ −42·1° (*c*, 0·99 in methanol) (Found: C, 40·8; H, 5·6. $C_9H_{15}O_4Br$ requires C, 40·4; H, 5·6%).

The 1-bromo-derivative (100 mg.) in dry pyridine (0·5 c.c.) was treated with toluene-*p*-sulphonyl chloride (1·5 mols.; 100 mg.) at 40° for 12 hours. Dilution with water afforded 4 : 5-iso*propylidene* 2-*toluene*-p-*sulphonyl* 3 : 6-*anhydro*-1-*bromo*-1-*deoxymannitol* (80 mg.) as fine colourless needles (from aqueous methanol), m. p. 86—87°, $[\alpha]_D^{20}$ −82·5° (*c*, 0·27 in ethanol) (Found: C, 46·0; H, 4·9; S, 7·7. $C_{16}H_{21}O_6BrS$ requires C, 45·6; H, 5·0; S, 7·6%).

Hydrogenation of Fraction A.—A solution of the 1-bromo-derivative (1·29 g.) in methanol (20 c.c.) was shaken in an atmosphere of hydrogen at a slight over-pressure in the presence of Raney nickel (2 g.) and diethylamine (0·4 g.). Hydrogen (90 c.c.; 1·3 mols.) was rapidly absorbed and after 2 hours the catalyst was collected and washed with hot methanol, and the combined filtrate and washings were evaporated to dryness, yielding a syrupy residue. From this was obtained 4 : 5-iso*propylidene* 3 : 6-*anhydro*-1-*deoxymannitol* (0·6 g.) as a colourless mobile liquid, b. p. 78—82° (bath-temp.)/0·01 mm., n^{22} 1·4554, $[\alpha]_D^{21}$ −62·9° (*c*, 1·09 in methanol) (Found: C, 56·7; H, 8·5. $C_9H_{14}O_4$ requires C, 57·4; H, 8·5%).

The 1-deoxy derivative (0·1 g.) gave, as in the foregoing case, the 2-*toluene*-p-*sulphonate* (0·115 g.), as colourless prisms (from aqueous methanol), m. p. 70—71°, $[\alpha]_D^{20}$ −70·1° (*c*, 0·54 in chloroform) (Found: C, 56·2; H, 6·4. $C_{16}H_{22}O_6S$ requires C, 56·1; H, 6·4%).

Iodine non-exchange. 4 : 5-*iso*Propylidene 2-toluene-*p*-sulphonyl 3 : 6-anhydro-1-deoxymannitol (30 mg.) and an excess of sodium iodide (50 mg.) were heated in dry acetone (2 c.c.) at 110—115° for 4 hours. There was no precipitation of sodium toluene-*p*-sulphonate.

Identification of Fraction B.—Fraction B (0·62 g.) gave a positive test for halogen and was soluble in water; it was essentially 3 : 6-anhydro-1-bromo-1-deoxymannitol. The syrup (0·6 g.) was shaken in methanol (20 c.c.) under hydrogen at a slight over-pressure in the presence of Raney nickel (1 g.). Hydrogen (50 c.c.) was rapidly absorbed and after 2 hours the catalyst was collected and washed with hot methanol, and the combined filtrate and washings were evaporated to dryness. The syrupy residue so obtained (0·34 g.) was shaken in acetone (50 c.c.) containing concentrated sulphuric acid (0·1 c.c.) for 24 hours. Neutralisation with sodium carbonate and evaporation afforded a syrup (0·35 g.). Treatment of this in dry pyridine (1·5 c.c.) with toluene-*p*-sulphonyl chloride (1·4 mols.; 0·5 g.) at room temperature for 24 hours, followed by dilution with water and recrystallisation of the solid product, gave 4 : 5-*iso*propylidene 2-toluene-*p*-sulphonyl 3 : 6-anhydro-1-deoxymannitol (0·4 g.), m. p. 70—71° alone or on admixture with the compound derived from fraction A.

Hydrolysis of 4 : 5-iso*Propylidene* 3 : 6-*Anhydro*-1-*deoxymannitol.*—A solution of the *iso*propylidene derivative (0·32 g.) in methanol (25 c.c.) containing 5N-hydrochloric acid (3 c.c.) was boiled under reflux. The hydrolysis was followed polarimetrically and shown to be complete in 1·5 hours. The acid was neutralised with silver carbonate, and the silver residues were removed in the usual manner. Evaporation of the solution gave a syrup which was purified by passage in methanol through a column of alumina (3 × 1 cm.). Evaporation of the eluate gave 3 : 6-*anhydro*-1-*deoxymannitol* as a colourless syrup, n^{18} 1·4757, $[\alpha]_D^{20}$ −34·0° (*c*, 0·74 in methanol) (Found: C, 48·5; H, 8·3. $C_6H_{12}O_4$ requires C, 48·6; H, 8·1%).

Action of Water on 4 : 5-iso*Propylidene* 1 : 2-3 : 6-*Dianhydromannitol.*—A solution of the dianhydro-compound (0·2 g.) in water (10 c.c.) was boiled under reflux for 8 hours. Evaporation of the solvent under diminished pressure gave a syrup which was dried over phosphoric oxide *in vacuo*. Recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave a product, m. p. 83—84° alone or on admixture with authentic 4 : 5-*iso*propylidene 3 : 6-anhydromannitol (Foster and Overend, *loc. cit.*).

Action of Lithium Aluminium Hydride on 4 : 5-iso*Propylidene* 1 : 2-3 : 6-*Dianhydromannitol.*—The dianhydro-compound (0·8 g.) in dry ether (20 c.c.) was added gradually to a mixture of finely powdered lithium aluminium hydride (1·3 g.) and ether (40 c.c.). The whole was boiled under reflux for 3 hours and then treated with ice-cold sulphuric acid until acidic to litmus. Excess of acid was neutralised with sodium carbonate, and the precipitated inorganic material collected and washed with acetone. The combined filtrate and washings were extracted four times with an equal volume of chloroform, and the combined extracts dried ($MgSO_4$) and evaporated to dryness. Distillation of the syrupy residue gave 4 : 5-*iso*propylidene 3 : 6-anhydro-1-deoxymannitol (0·55 g.) as a colourless mobile liquid, b. p. 80—85° (bath-temp.)/0·01 mm., n^{18} 1·4560, $[\alpha]_D^{20}$ −61° (*c*, 0·83 in methanol). Treatment of the substance (0·1 g.) in dry pyridine (0·4 c.c.) with toluene-*p*-sulphonyl chloride (0·15 g.) at room temperature for 20 hours, followed by working up in the usual manner, gave a crystalline substance, m. p. 70—71° alone or on admixture with 4 : 5-*iso*propylidene 2-toluene-*p*-sulphonyl 3 : 6-anhydro-1-deoxymannitol described above.

Action of Methylmagnesium Iodide on 4 : 5-iso*Propylidene* 1 : 2-3 : 6-*Dianhydromannitol.*—To a solution of methylmagnesium iodide prepared from magnesium (0·3 g.), methyl iodide (0·75 c.c.), and dry ether (5 c.c.), a solution of the dianhydro-compound (1·0 g.) in dry ether (10 c.c.) was added gradually during 30 minutes, with continual refluxing of the mixture. After a further 3 hours the ethereal solution was poured into ice-cold dilute sulphuric acid, and the aqueous layer extracted with chloroform (3 times; total volume 90 c.c.). The combined extracts were washed with dilute aqueous sodium hydrogen carbonate, dried ($MgSO_4$), and evaporated. The syrupy residue gradually crystallised and recrystallisation from light petroleum (b. p. 40—60°) gave 4 : 5-iso*propylidene* 3 : 6-*anhydro*-1-*deoxy*-1-*iodomannitol* (1·2 g.) as colourless prisms, m. p. 75—76°, $[\alpha]_D^{20}$ −44·6° (*c*, 0·99 in chloroform) (Found: C, 34·2; H, 4·9; I, 40·6. $C_9H_{15}O_4I$ requires C, 34·4; H, 4·8; I, 40·4%).

A solution of the iodo-compound (0·3 g.) in methanol (30 c.c.) was shaken in an atmosphere of hydrogen at a slight overpressure in the presence of Raney nickel (0·5 g.) and diethylamine (0·5 c.c.); rapid absorption of hydrogen occurred and after 1 hour the catalyst was collected and washed with methanol. Evaporation of the combined filtrate and washings gave a syrupy residue from which

4 : 5-*iso*propylidene **3** : 6-anhydro-1-deoxymannitol (0·1 g.) was obtained as a colourless mobile liquid, b. p. 75—80° (bath temp.)/0·01 mm., n^{21} 1·4550, $[\alpha]_D^{20}$ −60° (*c*, 1·0 in methanol).

Treatment of the 1-deoxy-derivative with toluene-*p*-sulphonyl chloride in the usual manner gave a crystalline product, m. p. 70—71° alone or on admixture with authentic **4** : 5-*iso*propylidene 2-toluene-*p*-sulphonyl **3** : 6-anhydro-1-deoxymannitol described above.

Action of Sodium Methoxide on **4** : 5-iso*Propylidene* **1** : **2-3** : **6-***Dianhydromannitol.*—A solution of the dianhydro-compound (0·84 g.) in methanol (30 c.c.) in which sodium (0·6 g.) had been dissolved was boiled under reflux for 30 hours. The solution was diluted with chloroform (100 c.c.), washed twice with water, dried ($MgSO_4$), and evaporated. Distillation of the syrupy residue thereby obtained gave 1-methyl **4** : 5-*iso*propylidene **3** : 6-anhydromannitol (0·69 g.) as a colourless hygroscopic liquid, n^{18} 1·4585, $[\alpha]_D^{20}$ −47·3° (*c*, 0·76 in methanol). The hygroscopic nature of this substance did not facilitate good analytical results (Found : C, 53·5; H, 8·6. Calc. for $C_{10}H_{18}O_5$: C, 55·0; H, 8·3%) but its identity was substantiated on conversion into its toluene-*p*-sulphonate. Toluene-*p*-sulphonyl chloride (1·5 mols., 0·45 g.) was added to a solution of the methyl derivative (0·3 g.) in dry pyridine (1·5 c.c.) and the mixture set aside at 35° for 18 hours. Dilution with water afforded a syrupy product which solidified on storage. Recrystallisation from aqueous methanol gave 1-*methyl* **4** : 5-iso*propylidene* 2-*toluene*-p-*sulphonyl* **3** : 6-*anhydromannitol* (0·3 g.) as colourless prisms, m. p. 82—83°, $[\alpha]_D^{20}$ −51·5° (*c*, 0·805 in chloroform) (Found : C, 54·6; H, 6·3. $C_{17}H_{24}O_7S$ requires C, 54·8; H, 6·5%).

Iodine non-exchange. A solution of the forgoing toluene-*p*-sulphonyl derivative (0·2 g.) in dry acetone (10 c.c.) containing sodium iodide (0·5 g.) was heated at 125—130° for 10 hours. There was no precipitation of sodium toluene-*p*-sulphonate.

Action of Methanolic Ammonia on **4** : 5-iso*Propylidene* **1** : **2-3** : **6-***Dianhydromannitol.*—The dianhydro-compound (0·25 g.) was treated with methanol (10 c.c.), saturated at 0° with ammonia, at 110—120° for 20 hours. The solution was evaporated to dryness, and the brown syrupy residue dissolved in ethanol and passed down a column of activated alumina (3 × 1 cm.), which removed coloured impurities. Evaporation of the eluate gave **4** : 5-iso*propylidene* 1-*amino*-**3** : 6-*anhydro*-1-*deoxymannitol* (0·24 g.) as a viscous straw-coloured syrup, n^{15} 1·4610, $[\alpha]_D^{20}$ −36·9° (*c*, 0·52 in ethanol) (Found : C, 53·3; H, 8·0. $C_9H_{17}O_4N$ requires C, 53·2; H, 8·4%).

The authors thank Professor M. Stacey, F.R.S., for his interest in this work and Miss Patricia M. Hudson for experimental assistance. One of them (A. B. F.) thanks to the Brewing Industry Research Foundation for financial assistance enabling him to complete this work.

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NOTES.

248. *The Synthesis of* 2 : 6-*Dicyano*-3 : 5-*dimethylaniline.*

By R. Hull.

A new aromatic compound has been obtained during an investigation into the preparation of 2-amino-3-cyano-4 : 6-dimethylpyridine from aliphatic intermediates.

Moir (*J.*, 1902, 113) and Knoevenagel and Cremer (*Ber.*, 1902, **35**, 2393) prepared 3-cyano- and 3-carbethoxy-2-hydroxy-4 : 6-dimethylpyridines by reaction of 1-acetyl-2-aminopropene with cyanoacetamide and malonic ester, respectively. Reaction of 1-acetyl-2-aminopropene and malononitrile, however, has now given two products.

One of these compounds, $C_8H_8ON_2$, m. p. 289—290°, which was soluble in alkali, was 5 : 5-dicyano-2-hydroxy-4-methylpenta-2 : 4-diene, for on hydrolysis with sulphuric acid it gave a degradation product, C_7H_9ON, undepressed in melting point on admixture with 2-hydroxy-4 : 6-dimethylpyridine (Knoevenagel and Cremer, *loc. cit.*). The other product, $C_{10}H_8N_2$, m. p. 211—213°, gave, on acid hydrolysis, a liquid primary arylamine, $C_8H_{11}N$, b. p. 221—222°/752 mm., and a solid, $C_9H_{12}ON_2$, m. p. 160°. The liquid was identified as 3 : 5-dimethylaniline by its physical properties and the formation of 5-*p*-sulphanilamido-*m*-xylene. The product, $C_{10}H_8N_2$, was therefore 2 : 6-dicyano-3 : 5-dimethylaniline, and the solid hydrolysis product, $C_9H_{12}ON_2$, 2-carbamyl-3 : 5-dimethylaniline.

2 : 6-Dicyano-3 : 5-dimethylaniline was probably formed by condensation of the dimer of malononitrile with 1-acetyl-2-aminopropene, with subsequent elimination of cyanamide. 5 : 5-Dicyano-2-hydroxy-4-methylpenta-2 : 4-diene was not an intermediate in the formation of the aniline, because reaction of the aliphatic compound with a further molecular proportion of malononitrile gave no formation of the aromatic compound.

The same products were formed, in the presence of alkali, from acetylacetone and malononitrile. This reaction was mentioned by Östling (*Oversikt Finska Vet. Soc. Forhändl.*, 1915, **57** *A*, No. 11) but no details were given of any compounds isolated.

Experimental.—Condensation of 1-acetyl-2-aminopropene and malononitrile. 1-Acetyl-2-aminopropene (25·7 g., 0·26 mol.) (Combes, *Bull. Soc. chim.*, 1892, **7**, 779) was added to a stirred suspension of malononitrile (18·9 g., 0·268 mol.) in water (200 c.c.), and stirring continued 18 hours. After a further 2 days the solid (25 g.) was collected and washed with water. The material [m. p. 204—225° (sintering 195°)] was extracted with 2N-sodium hydroxide (100 c.c.). The insoluble product (13·5 g.), m. p. 210—212°, on crystallisation from aqueous alcohol gave needles, m. p. 211—213°, of *2 : 6-dicyano-3 : 5-dimethylaniline* (Found : C, 70·0; H, 5·15; N, 24·55. $C_{10}H_9N_3$ requires C, 70·2; H, 5·25; N, 24·6%). The alkaline extract was acidified with 5N-hydrochloric acid, and the precipitate (11·5 g.) crystallised from alcohol, giving needles, m. p. 289—290°, of *5 : 5-dicyano-2-hydroxy-4-methylpenta-2 : 4-diene* (Found : C, 64·7; H, 5·3; N, 19·3. $C_9H_8ON_2$ requires C, 64·85; H, 5·4; N, 18·9%).

When 1-acetyl-2-aminopropene (9·9 g., 0·1 mol.) and malononitrile (13·2 g., 0·2 mol.) were used 2 : 6-dicyano-3 : 5-dimethylaniline (6·6 g.), m. p. 210—211°, and 5 : 5-dicyano-2-hydroxy-4-methylpenta-2 : 4-diene (4·6 g.), m. p. 289—290°, were again produced.

Condensation of acetylacetone and malononitrile. 5N-Sodium hydroxide (10 c.c.) was slowly run into a stirred mixture of acetylacetone (20 g., 0·2 mol.) and malononitrile (26·4 g., 0·4 mol.) in water (200 c.c.), and stirring was continued for 4 hours. The solid was collected, washed with water, and separated by treatment with dilute alkali, giving 5 : 5-dicyano-2-hydroxy-4-methylpenta-2 : 4-diene (19·8 g.), m. p. 287—288°, and 2 : 6-dicyano-3 : 5-dimethylaniline (3·4 g.), m. p. 213—215°.

Hydrolysis of 2 : 6-dicyano-3 : 5-dimethylaniline. 2 : 6-Dicyano-3 : 5-dimethylaniline (2·9 g.) was heated under reflux with 50% sulphuric acid (15 c.c.) for 6 hours. The reaction mixture was made alkaline with sodium hydroxide and ether extracted. Evaporation of the solvent and distillation gave 3 : 5-dimethylaniline, b. p. 221—222°/750 mm. This was purified for analysis by being refluxed over solid sodium hydroxide and redistilled [Found : C, 79·2; H, 8·9; N, 11·6%; *M* (nitrite titration), 120·6. Calc. for $C_8H_{11}N$: C, 79·35; H, 9·1; N, 11·55%; *M*, 121]. Recrystallisation from alcohol of the residue from the first distillation gave needles of *2-carbamyl-3 : 5-dimethylaniline*, m. p. 160° (Found : C, 65·95; H, 7·6; N, 16·9. $C_9H_{12}ON_2$ requires C, 65·85; H, 7·3; N, 17·1%).

3 : 5-Dimethylaniline (2·05 g.), from a second hydrolysis, *p*-acetamidobenzenesulphonyl chloride (2·74 g.), and pyridine (4 c.c.) were heated, with stirring, at 60—70° for 1 hour and then at 40° for 16 hours. The mixture was diluted with water and stirred for 18 hours, and the aqueous supernatant liquor then decanted off. The solid, after being washed, was refluxed gently with N-hydrochloric acid (20 c.c.) for 7 hours, cooled and filtered, the filtrate was made alkaline with ammonia solution, and the product collected. Recrystallisation from aqueous alcohol gave prismatic needles, m. p. 145—147° undepressed on admixture with authentic *5-p*-sulphanilamido-*m*-xylene.

Acid hydrolysis of 5 : 5-dicyano-2-hydroxy-4-methylpenta-2 : 4-diene. 5 : 5-Dicyano-2-hydroxy-4-methylpenta-2 : 4-diene (1·0 g.) and 50% sulphuric acid (4·3 c.c.) were heated under reflux for 6 hours. The mixture was neutralised with sodium hydroxide and then made slightly alkaline with ammonia solution. The solid was collected and crystallised from water giving 2-hydroxy-4 : 6-dimethylpyridine as feathery needles, m. p. 173—175°. Sublimation raised the m. p. to 177—178°, undepressed with an authentic specimen (Moir, *loc. cit.*) (Found : C, 68·05; H, 7·2; N, 11·7. Calc. for C_7H_9ON : C, 68·3; H, 7·3; N, 11·4%).

IMPERIAL CHEMICAL INDUSTRIES LIMITED,
RESEARCH LABORATORIES, BLACKLEY, MANCHESTER, 9. [*Received, January 12th*, 1951.]

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249. *The Oxidation of* 4 : 11-*Dibromofluoranthene.*

By NEIL CAMPBELL, W. H. STAFFORD, and J. F. K. WILSHIRE.

IT was shown (Campbell, Easton, Rayment, and Wilshire, *J.*, 1950, 2784) that chromic acid oxidation of dibromofluoranthene yields 2 : 7-dibromofluorenone-1-carboxylic acid and a monobromo-acid provisionally regarded as 6-bromofluorenone-1-carboxylic acid (II). We have now

confirmed this formulation by decarboxylation of the acid to 3-bromofluorenone, showing that the acid (II) is formed by oxidation of the ring A (I) and providing further evidence that the original compound is 4 : 11-dibromofluoranthene (cf. Holbro and Tagmann, *Helv. Chim. Acta*, 1950, **33**, 2178).

Experimental.—The mixture of acids obtained by oxidation of dibromofluoranthene was boiled with successive 500-ml. portions of calcium hydroxide solution and the hot solutions were filtered. The cold filtrates deposited the calcium salt of the dibromo-acid and the filtrate on acidification gave 6-bromofluorenone-1-carboxylic acid, which crystallised in yellow rosettes, m. p. 253—255°, from glacial acetic acid and gave a *methyl* ester, m. p. 126—127° (Found: Br, 25·8. $C_{15}H_9O_3Br$ requires Br, 25·2%).

The acid on decarboxylation with quinoline and copper-bronze afforded 3-bromofluorenone, yellow leaflets (from light petroleum), m. p. 162—163°, undepressed on admixture with an authentic sample Found: Br, 31·2. Calc. for $C_{13}H_7OBr$: Br, 30·9%). This substance was prepared from *o*-(4-bromobenzoyl)benzamide by Miller and Bachman's method (*J. Amer. Chem. Soc.*, 1935, **57**, 2443), but we were unable to attain the high yields reported by them. By adding a benzene solution of the acid chloride to saturated methanolic ammonia we prepared the substituted benzamide, and after repeated crystallisation from xylene, xylene–acetone, and acetic acid obtained it as needles, m. p. 224° (Found: N, 4·4; Br, 24·1. Calc. for $C_{13}H_{10}O_2NBr$: N, 4·6; Br, 26·3%). The substance is clearly not quite pure (probably owing to adhering solvent), but nevertheless it melts nearly 40° higher than Miller and Bachman's product (m. p. 184·5—185°), which we think was a mixture of acid and amide. The amide was converted *via* 2-amino-4′-bromobenzophenone, m. p. 112°, into 3-bromofluorenone, which had the m. p. given by other workers (*e.g.*, Heilbron, Hey, and Wilkinson, *J.*, 1938, 113).

Thanks are expressed to the Carnegie Trust for the Universities of Scotland for the award of a scholarship to one of us (W. H. S.), and to the Anglo-Iranian Oil Co. Ltd. for a grant.

UNIVERSITY OF EDINBURGH. [*Received, January 9th*, 1951.]

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250. *Some Hydroxyanthraquinones and Derivatives.*

By LINDSAY H. BRIGGS and G. A. NICHOLLS.

IN connection with investigations of the anthraquinone pigments from the bark of *Coprosma* species (cf. Briggs and Thomas, *J.*, 1949, 1246, and earlier papers) and the systematic study of the polarographic behaviour of anthraquinone derivatives (forthcoming communications) we have prepared the following compounds by new or modifications of existing methods.

2 : 6-*Dihydroxyanthraquinone.*—Although insoluble in acids, 2 : 6-diaminoanthraquinone may be diazotised and converted into the 2 : 6-dihydroxy-compound. An ice-cold aqueous solution (50 c.c.) of sodium nitrite (7 g., 2 mols.) was added to an ice-cold suspension of 2 : 6-diaminoanthraquinone (12 g., 1 mol.) in sulphuric acid (20 g. diluted with 100 c.c. of water; 4 mols.), and the mixture shaken for 10 minutes, warmed on the water-bath until most of the frothing had ceased (20 minutes), and finally boiled for 20 minutes. The yellowish-brown product was filtered off, boiled with barium hydroxide solution (17 g. in 250 c.c.) and filtered whilst hot. The precipitate was again extracted with boiling water (250 c.c.) and filtered. On acidification of the combined filtrates a yellow precipitate was formed which was well washed with water (yield, 4 g., 33%) and purified by chromatography of its acetone solution on magnesia from which it was recovered by dissolution of the magnesia in dilute hydrochloric acid. The product was crystallised twice from alcohol (charcoal), forming golden-yellow rods, m. p. >330° [Schunck and Roemer, *Ber.*, 1876, **9**, 379, and Heller, *Angew. Chem.*, 1929, **42**, 170, record m. p. >330° and 360° (decomp.), respectively].

The diacetate, prepared by acetylation of the above compound (37 mg.) with acetic anhydride (0·75 c.c.) and 60% perchloric acid (1 drop), crystallised from acetic anhydride in almost colourless plates of constant m. p. 233—234° (Perkin, *J.*, 1873, **26**, 19, records pale yellow crystals, m. p. 228—229°, for this derivative).

2 : 6-*Dimethoxyanthraquinone.*—2 : 6-Dihydroxyanthraquinone (43 mg.), in dry acetone (8 c.c.), was heated at 100° with methyl sulphate (0·5 c.c.) and anhydrous potassium carbonate for 2 hours. The mixture was poured into cold water (15 c.c.), the acetone removed by distillation, and the product collected as almost colourless plates, m. p. 257° unchanged on recrystallisation from glacial acetic acid. Schunck and Roemer (*loc. cit.*; cf. also D.R.P. 167699 1905) record yellow needles, m. p. 250°, from benzene.

Attempted Synthesis of 1 : 3 : 5-*Trihydroxyanthraquinone.*—A mixture of *m*-hydroxybenzoic acid (4·6 g., 1 mol.) and 3 : 5-dihydroxybenzoic acid (5·1 g., 1 mol.) was heated with concentrated sulphuric acid (18 c.c., 10 mols.) for an hour at 100°. Next morning, the mixture was heated at 140—150° for 10 minutes and the cooled reddish-brown solution poured into boiling water (300 c.c.). The green precipitate (2·6 g., 30%) was extracted with acetone leaving a black residue. Chromatography of the acetone solution on magnesia gave two main red and orange bands; decomposition of the red band with hydrochloric acid gave a bright green precipitate which, on being rechromatographed, afforded red and orange bands identical in appearance with those of the first chromatogram, a phenomenon which was reproduced on repeating the cycle. However, by repeated dissolution of the green precipitate in aqueous sodium hydroxide solution, and reprecipitation from the hot solution with glacial acetic acid, a yellow product was finally obtained, giving an orange band on a magnesia column. After rechromatographing the material from the combined orange bands, pure anthrachrysone (1 : 3 : 5 : 7-tetrahydroxyanthraquinone) was obtained, crystallising from alcohol in yellow needles which sublimed, but did not melt below 350° (Noah, *Ber.*, 1886, **19**, 751, records yellow needles, m. p. >360°). The sodium hydroxide, sodium carbonate, and concentrated sulphuric acid solutions were red; and a brown colour was given with ferric chloride solution.

The tetra-acetate, prepared by acetylation with acetic anhydride and 60% perchloric acid, crystallised from acetic anhydride in pale-cream rods which slowly decomposed at 239°, but when heated quickly melted at 259° (decomp.) (Noah, *loc. cit.*, and Lauer, *J. pr. Chem.*, 1932, **135**, [ii], 361, record m. p. 254—256°).

Anthrachrysone tetrabenzoate was obtained as pale-cream rods, m. p. 280—283·5°, from dioxan (Found: C, 72·55; H, 3·9. $C_{42}H_{24}O_{10}$,0·5H_2O requires C, 72·3; H, 3·6%).

Anthrachrysone Tetramethyl Ether.—This was prepared as described above for 2 : 6-dimethoxyanthraquinone, the mixture being heated under reflux for 2 hours. The m. p. of the product (291—293°) confirms that given by Fischer and Ziegler (*J. pr. Chem.*, 1912, **86**, [ii], 297) but is not in agreement with that recorded by Heller ("Elsevier's Encyclopædia of Organic Chemistry," Vol. 13, p. 607). This derivative is insoluble in alkali and almost insoluble in acetone.

Anthrachrysone 3 : 7-*Dimethyl Ether.*—Anthrachrysone (214 mg.), dry acetone (15 c.c.), anhydrous potassium carbonate (4 g.), and methyl sulphate (0·5 c.c.) were heated under reflux for 10 minutes. The product (100 mg.), obtained in this case from the carbonate by treatment with acid, formed, after two crystallisations from nitrobenzene, intensely yellow plates, m. p. 287—288° (with sublimation) (Found: C, 64·0; H, 4·3. Calc. for $C_{16}H_{12}O_6$: C, 64·0; H, 4·0%). The compound forms an insoluble sodium salt with aqueous sodium hydroxide solution. Fischer and Ziegler (*loc. cit.*) record bronze prisms, forming a yellowish-red solution in alkali, but they give no m. p.

Purpurin trimethyl ether. Purpurin (240 mg.) was similarly methylated with methyl sulphate (1 c.c.), more methyl sulphate (0·5 c.c.) being added after an hour and the heating then continued for 3½ hours. The crude product (300 mg.) was purified by chromatography on magnesia; and the *ether* was obtained as yellow rods, which were recrystallised from 80% alcohol and ethyl acetate. It had m. p. 169—171° (Found: C, 68·2; H, 4·6. $C_{17}H_{14}O_5$ requires C, 68·4; H, 4·7%).

The analyses are by Drs. Weiler and Strauss, Oxford, and Dr. T. S. Ma, Microchemical Laboratory, Otago University, Dunedin.

The authors are indebted to the Chemical Society, the Australian and New Zealand Association for the Advancement of Science, the Royal Society of New Zealand, and the Research Fund Committee of the University of New Zealand for continued grants, and to Imperial Chemical Industries Limited for gifts of chemicals; one of them (G. A. N.) expresses gratitude for a Research Fellowship of the University of New Zealand.

AUCKLAND UNIVERSITY COLLEGE, AUCKLAND, NEW ZEALAND. [*Received, December 29th*, 1950.]

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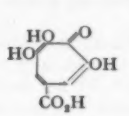
251. *Puberulic and Puberulonic Acids. Part III. The Structure of Puberulonic Acid.*

By A. W. JOHNSON, N. SHEPPARD, and A. R. TODD.

IN previous publications (Corbett, Johnson, and Todd, *Chem. and Ind.*, 1949, 626; *J.*, 1950, 6) evidence was presented showing that puberulic acid had structure (I), and it was suggested on the then available facts that puberulonic acid might be represented by one of the lactonic structures (II) or (III). Structures of this type were advanced to explain (*a*) the yellow colour of the acid, (*b*) its condensation with *o*-phenylenediamine to a highly-coloured product, $C_{18}H_8O_5N_2$, considered to be a quinoxaline derivative (Corbett, Hassall, Johnson, and Todd, *J.*, 1950, 1), (*c*) its ready conversion into puberulic acid on being heated with water or dilute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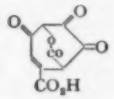
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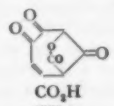
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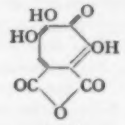
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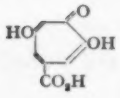
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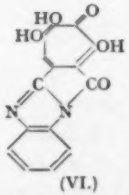
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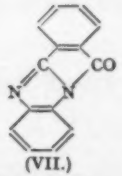
(VII.)

acids, and (*d*) its failure to acetylate with acetic anhydride under conditions which readily effected acetylation of puberulic acid (Birkinshaw and Raistrick, *Biochem. J.*, 1932, **26**, 441). The titration curve of puberulonic acid suggested the presence in it of a lactone or other potential acid group. Lack of material prevented further work on puberulonic acid until recently, and in the meantime, Aulin-Erdtman, on the basis of an extensive study of the ultra-violet absorption of the acid at various pH values, maintained that it must contain an actual, rather than a

potential, tropolone system, and suggested for it the anhydride structure (IV) (Chemical Society Symposium on Tropolones, London, 2nd November, 1950).

In collaboration with Dr. P. W. Brian and Mr. P. J. Curtis of Imperial Chemical Industries Limited, Butterwick Research Laboratories, Welwyn, we have prepared a further quantity of puberulonic acid and find that its infra-red spectrum supports Aulin-Erdtman's structure (IV) in every respect. The main strong frequencies in the 1500—1900-cm.$^{-1}$ region were as follows, the values for puberulic acid and stipitatic acid (V) being given for comparison.

Puberulonic acid	1545	1615	—	1770	1830
Puberulic acid	1535	1595	1690	—	—
Stipitatic acid	1570	1610	1705	—	—

The first two absorption bands have been assigned (Scott and Tarbell, *J. Amer. Chem. Soc.*, 1950, **72**, 240; see also Bartels-Keith and Johnson, *Chem. and Ind.*, 1950, 677) to the basic tropolone structure; the frequency range 1720—1680 cm.$^{-1}$ is generally considered to be characteristic of the C=O group in an acid (*i.e.*, absent in puberulonic acid), and the two bands above 1750 cm.$^{-1}$ are characteristic of the anhydride system (Randall, Fowler, Fuson, and Dangl, "Infra-red Determination of Organic Structures," New York, 1949, p. 20). Confirmatory evidence is available in the 3000-cm.$^{-1}$ region characteristic of O–H groups. Unlike puberulonic acid, puberulic and stipitatic acids show weak, broad absorption bands centred near 2700 cm.$^{-1}$, which may be the strongly bonded O–H groups of the acid dimer. Furthermore, puberulonic acid shows an absorption band between 3100 and 3200 cm.$^{-1}$ which is consistent with the presence of hydroxy-groups in the tropolone nucleus.

The absorption spectra leave little doubt as to the correctness of structure (IV) for puberulonic acid, and the evidence on which the lactone structures (II) and (III) were based must be reconsidered. The anhydride structure (IV) accommodates the required potential acid grouping just as well as a lactone structure and gives an equally ready explanation for the conversion into puberulic acid; that the anhydride ring always re-forms immediately when alkaline solutions of puberulonic acid are acidified is unusual but no more. The yellow colour of puberulonic acid can be ascribed to the anhydride grouping, and it may be recalled that similar deepening of colour in passing from a dicarboxylic acid to its anhydride has been observed in the fulgenic acid–fulgide series (*e.g.*, Stobbe, *et al.*, *Annalen*, 1908, **359**, 2; 1911, **380**, 120). The condensation product with *o*-phenylenediamine is clearly not a quinoxaline. Its structure has not been determined but is probably of type (VI); this would account for our failure to decarboxylate it (cf. Corbett, Johnson, and Todd, *loc. cit.*). Compounds [*e.g.*, *o*-benzoylene-1 : 2-benziminazole (VII)] analogous to (VI) have been isolated from the products of reaction of *o*-phenylenediamine with various anhydrides (Lieb, *Monatsh.*, 1918, **39**, 873; Bistrzycki and Fässler, *Helv. Chim. Acta*, 1923, **6**, 519). The failure of puberulonic acid to acetylate is rather unexpected on the basis of structure (IV), and it seems possible that the preparation of an acetyl derivative may yet be effected under special conditions.

While this note was in preparation, we learned from Woodward, Hassall, and Sondheimer that they had independently reached the same conclusion regarding the correctness of structure (IV) and on the same evidence. We thank Professor R. B. Woodward for his courtesy in sending us an account of his findings. Correspondence with Mrs. G. Aulin-Erdtman revealed that she, too, has determined the infra-red spectrum of puberulonic acid and her results are in the course of publication.

University Chemical Laboratory, Cambridge. [*Received, January 8th*, 1951.]

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252. *The* N-*Toluene*-p-*sulphonyl Derivatives of the* p-*Halogenoanilines.*

By J. Ratcliffe.

The melting point of toluene-*p*-sulphon-4-chloroanilide has been reported as 95° (Chattaway, *J.*, 1904, **85**, 1181) and 119° (D.R.-P. 164,130; *Chem. Zentr.*, 1905, II, 1476). The higher m. p. is also recorded by Curd and Rose (*J.*, 1946, 734), but had been disputed by Halberkann (*Ber.*, 1921, **54**, 1846). This compound and the bromo- and iodo-analogues have been prepared in another connection with the following result. The chloro-compound formed prismatic needles, m. p. 95°, from aqueous ethanol in the cold (cf. Chattaway and Halberkann, *locc. cit.*), but had m. p. 122° when formed (as needles) from hot ethanol or when grown slowly (as large colourless

prisms) from cold ethanol; the bromo-compound had m. p. 102°, small colourless prismatic needles from aqueous ethanol, or m. p. 149°, colourless prismatic needles from hot ethanol and large prisms from cold ethanol; the iodo-compound had m. p. 96°, fine needles from aqueous ethanol, or m. p. 171°, fine needles from ethanol. As noted by Halberkann, a change of solvent altered the crystal habit.

On storage, the lower-melting forms changed in all three cases to the higher-melting variety but no corresponding changes in crystal form were revealed under the microscope. Lower-melting forms could not be produced from apparatus contaminated with the corresponding form of higher m. p. Toluene-*p*-sulphon-4-bromoanilide, m. p. 102°, dissolved readily in cold sodium hydroxide solution, but the solution frequently deposited a less soluble sodium derivative of the higher-melting form which furnished the form of m. p. 149° on treatment with mineral acid, and reverted to the insoluble sodium derivative, which did not melt below 300°, in alkali. The higher-melting form did not respond to attempts to reconvert it into the one of lower m. p.

Experimental.—The lower-melting forms could be obtained as follows: The appropriate *p*-halogenoaniline (0·1 g.-mol.) in solution in 30 ml. of pyridine was slowly treated with the calculated amount of toluene-*p*-sulphonyl chloride. Heat was generated and a red fluorescence developed which diminished during 30 minutes' heating on a water-bath. After removal of pyridine by hydrochloric acid, the residual oil or paste was taken up in cold ethanol, water was added to faint turbidity, and the solution refrigerated. The crystalline deposits from several such dilutions were collected (total yield 80—90%) and recrystallised to attain the m. p.s quoted. Dissolution of the crude products in cold sodium hydroxide solution with the object of eliminating the ditoluene-*p*-sulphonyl derivatives contributed little to the purity of the products and involved the risk of change to the higher-melting form, particularly for the bromo-compound as indicated above.

To prepare the forms of higher m. p., it is only necessary to contaminate the apparatus beforehand with this form and proceed as before, the deposits then solidifying readily on dilution of the pyridine and stirring.

Toluene-*p*-sulphon-4-chloroanilide had m. p. 122° (Found: Cl, 12·5; S, 11·4. Calc. for $C_{13}H_{12}O_2NClS$: Cl, 12·6; S, 11·4%); the *bromoanilide* had m. p. 149° (Found: Br, 24·4; S, 9·7. $C_{13}H_{12}O_2NBrS$ requires Br, 24·5; S, 9·8%), and the *iodoanilide* m. p. 171° (Found: I, 33·9; S, 8·5. $C_{13}H_{12}O_2NIS$ requires I, 34·05; S, 8·6%). These analyses relate to forms of low m. p. which had been left to attain the higher m. p.

By stopping the condensation of *p*-bromoaniline at an early stage, dilution with water, and extraction with ethanol, hair-like red needles were deposited, m. p. 131°. At the m. p. these red needles lose colour, which is partly restored by immediately stopping the heating, but further heating results in a colourless product, m. p. 149°, identified as toluene-*p*-sulphon-4-bromoanilide. The red needles appear to be an intermediate product containing pyridine which is driven off by heat. The amount of this red compound which could be isolated was too small for fuller investigation.

SOUTH EAST ESSEX TECHNICAL COLLEGE, DAGENHAM. [*Received, December 8th*, 1950.]

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253. *The Preparation and Properties of* tert.*-Butyl Bromide.*

By D. BRYCE-SMITH and K. E. HOWLETT.

IN connection with another research, pure *tert.*-butyl bromide was required; but none of the methods of preparation described in the literature (Norris, *Amer. Chem. J.*, 1907, **38**, 641; *Org. Synth.*, Coll. Vol. 1, p. 38) appeared entirely satisfactory. In particular, Norris has reported a yield of 90%, but in our hands his procedure has given about 40% yield of impure product. We have found the following to be a superior method of preparation.

Experimental.—*tert.*-Butyl alcohol (118 g., 1·6 g.-mols.) was added with stirring during 15 minutes to a mixture of hydrobromic acid (370 c.c. of 48% w/w solution; 3·2 g.-mols.) and concentrated sulphuric acid (100 c.c.), and the temperature was maintained at 20°. After a further 30 minutes, the organic layer was separated, washed twice with water, and dried (calcium chloride plus a trace of calcium oxide). On distillation, the first fraction (a few c.c.) contained dissolved *iso*butene and was rejected. The bulk (186 g., 85%) of the distillate had b. p. 53°/400 mm., and there was no appreciable distillation residue. The product showed no unsaturation when tested with bromine in carbon tetrachloride and had f. p. −16·4° to −16·7°. The use of twice the quantity of sulphuric acid increased the yield to 90%, but this slight increase scarcely justifies the use of such an excess.

The product obtained at this stage is of suitable purity for normal synthetic work. Further purification was, however, effected by fractional crystallisation. This process, repeated four times, raised the f. p. to −16·3°, whilst the purified product and rejected matter differed in n_D^{20} values by only 0·0002. Good freezing "flats" were obtained in the last two crystallisations. These determinations show that no appreciable isomerisation occurs in the preparation since the isomeric bromobutanes differ markedly from the tertiary compound in freezing point and refractive index. The yield of pure product was 65%, based upon the *tert.*-butyl alcohol used. Pure *tert.*-butyl bromide slowly decomposes when

kept; the decomposition appears to be retarded by the addition of about 0·1% of calcium oxide and storage in the dark at a low temperature.

The following physical constants were obtained for pure *tert.*-butyl bromide (cf. Timmermans, "Physico-Chemical Constants of Pure Organic Compounds," Elsevier, 1950, p. 268): b. p_{760} 72·8° (with slight decomp.); f. p. −16·3° (sulphur dioxide vapour-pressure thermometer); d_4^{20} 1·2125 g./c.c.; n_D^{20} 1·4249.

T°.	Vapour pressure.	*T*°.	Vapour pressure.	*T*°.	Vapour pressure.
0·0	42·8	22·7	121·9	40·0	243·4
6·8	59·0	25·0	135·3	49·3	344·5
10·6	70·7	28·4	155·4	56·6	450·4
15·7	90·0	31·3	174·5	63·5	567·6
20·8	112·9	35·7	209·3	72·8	758·0

The vapour pressure of *tert.*-butyl bromide was measured, an isoteniscope being used, over the range 0—73°. The results, given in the table, can be expressed by the equation $\log_{10} p = 7·627 - 1640/T$, whence the Trouton constant is 21·1.

BEDFORD COLLEGE (UNIVERSITY OF LONDON), LONDON, N.W.1.

[*Received, December 15th*, 1950.]

254. *A Synthesis of α-Amino-β-3-indenylpropionic Acid.*

By L. H. GROVES and G. A. SWAN.

3-BROMOMETHYLINDENE (Clemo, Groves, Munday, and Swan, *J.*, 1951, 863) was condensed with ethyl formamidomalonate and the product hydrolysed and decarboxylated to give α-amino-β-3-indenylpropionic acid (inset), an analogue of tryptophan.

Mr. T. K. Miller, of the Department of Bacteriology, King's College, Newcastle-on-Tyne, kindly investigated the effect of this amino-acid on the growth of *Lactobacillus arabinosus*, for which tryptophan is an essential metabolite, and found that it could neither replace nor antagonise tryptophan, the latter even in concentration ratios of 12 : 1 with respect to the indene-acid and tryptophan.

Experimental.—Ethyl α-carbethoxy-α-formamido-β-3-indenylpropionate. To a solution of sodium (0·25 g.) in absolute ethanol (20 ml.) were added ethyl formamidomalonate (2·23 g.) (Galat, *J. Amer. Chem. Soc.*, 1947, **69**, 965) and 3-bromomethylindene (2·3 g.), and the mixture kept at room temperature for 18 hours. It was then heated on the water-bath for a further 18 hours, the bulk of the ethanol removed by distillation, the residue treated with water, the mixture extracted with chloroform, the extract dried (Na_2SO_4), and the solvent removed. The residue (2·3 g.) on recrystallisation from dilute ethanol gave the *diester* as short colourless needles (1·95 g.), m. p. 102—103° (Found: C, 65·1; H, 6·3. $C_{18}H_{21}O_5N$ requires C, 65·25; H, 6·35%).

The above ester (1·0 g.) in 10% ethanolic potassium hydroxide (10 ml.) was heated under reflux for 30 minutes in an atmosphere of nitrogen. After cooling, water (50 ml.) was added and the solution washed successively with chloroform and ether. The ether was removed in a stream of air at room temperature, and the mixture was cooled in ice and acidified (dilute hydrochloric acid), giving the *dicarboxylic acid* (0·65 g.), m. p. 128—130° (decomp.). Recrystallisation from a small volume of ether afforded colourless plates, m. p. 133—134° (decomp.) (Found: C, 57·75; H, 4·8. $C_{14}H_{13}O_5N,H_2O$ requires C, 57·35; H, 5·1%).

α-Formamido-β-3-indenylpropionic acid. An almost theoretical yield of this *acid*, m. p. 161—163°, was obtained when the above dicarboxylic acid was heated at 100°/15 mm. for 1 hour. Recrystallisation from hot water afforded pale yellow needles, m. p. 163—164° (Found: C, 67·6; H, 5·95. $C_{13}H_{13}O_3N$ requires C, 67·55; H, 5·65%).

α-Amino-β-3-indenylpropionic acid. The formamido-acid (1·0 g.) in 4N-sulphuric acid (16 ml.) with a crystal of stannous chloride was heated on the water-bath for 3 hours in an atmosphere of nitrogen. The solution was diluted with water to 120 ml., boiled with charcoal, neutralised to pH 6—7 while hot with barium hydroxide, filtered from barium sulphate, and concentrated under reduced pressure until precipitation of the *amino-acid* (0·8 g.) occurred. The product was purified by dissolution in a large volume of water, boiling with charcoal, filtration, and concentration. It crystallised in granular clusters, m. p. 226—228° (decomp.) (Found: C, 70·8; H, 6·25. $C_{12}H_{13}O_2N$ requires C, 70·95; H, 6·4%).

The amino-acid (0·1 g.) was heated in anhydrous formic acid (0·3 ml.) for 3 hours at 100°, the solvent removed under reduced pressure, and this procedure twice repeated. The brown syrup remaining was boiled with water (5 ml.). The formyl derivative crystallised on cooling, and had m. p. 161—163°, not depressed on admixture with the amido-acid prepared as above.

Thanks are offered to the Department of Scientific and Industrial Research for a maintenance grant (to L. H. G.); and to Professor G. R. Clemo, F.R.S., for his interest.

UNIVERSITY OF DURHAM, KING'S COLLEGE,
NEWCASTLE-ON-TYNE, 1.

[*Received, October 21st*, 1950.]

THE CHEMICAL SOCIETY

SCIENTIFIC MEETINGS DURING MAY, 1951

LONDON.

Thursday, May 3rd, 1951, at 7.30 p.m.

Lecture, **Chemical Evidence Relative to the Origins of the Earth and Planets,** by Professor H. C. Urey, D.Sc., Ph.D., For.Mem.R.S. (Honorary Fellow of the Chemical Society).

To be given in Burlington House.

Thursday, May 10th, 1951, at 7.30 p.m.

Liversidge Lecture, **Transient Entities in Chemical Reactions,** by Professor H. W. Melville, D.Sc., F.R.S.

To be given in the Lecture Theatre, The Royal Institution, Albemarle Street, W.1.

BIRMINGHAM.

Friday, May 11th, 1951, at 4.30 p.m.

Lecture, **Recent Developments and Applications of Infra-red Spectroscopy,** by Dr. H. W. Thompson, M.A., F.R.S.

Joint meeting with the University Chemical Society to be held in the Lecture Theatre, Chemistry Department, The University, Edgbaston, Birmingham, 15.

GLASGOW.

Friday, May 11th, 1951, at 7.15 p.m.

Centenary Lecture, **Some Recent Advances in the Chemistry of Natural Products,** by Professor R. B. Woodward (Harvard).

To be given in the Chemistry Department, The University, Glasgow.

IRISH REPUBLIC.

Monday, May 21st, 1951, at 7.45 p.m.

Centenary Lecture, **Some Recent Advances in the Chemistry of Natural Products,** by Professor R. B. Woodward (Harvard).

To be given in the Department of Chemistry, Trinity College, Dublin.

Friday, May 25th, 1951, at 8 p.m.

Lecture, **Electron-transfer Reactions,** by Professor M. G. Evans, D.Sc., F.R.S.

Joint meeting with the Werner Chemical Society to be held in the Department of Chemistry, Trinity College, Dublin.

LIVERPOOL.

Thursday, May 17th, 1951, at 4.30 p.m.

Centenary Lecture, **Some Recent Advances in the Chemistry of Natural Products,** by Professor R. B. Woodward (Harvard).

To be given in the Chemistry Lecture Theatre, The University, Liverpool.

MANCHESTER.

Wednesday, May 16th, 1951, *at* 6.30 *p.m.*

Centenary Lecture, **Some Recent Advances in the Chemistry of Natural Products,** by Professor R. B. Woodward (Harvard).

To be given in the Chemistry Department, The University, Manchester.

NEWCASTLE AND DURHAM.

Wednesday, May 9th, 1951, *at* 5 *p.m.*

Centenary Lecture, **Some Recent Advances in the Chemistry of Natural Products,** by Professor R. B. Woodward (Harvard).

To be given in the Chemistry Building, King's College, Newcastle-on-Tyne.

Friday, May 11th, 1951, *at* 5 *p.m.*

Bedson Club Lecture, **Some Applications of Isotope Technique to the Study of Cel Metabolism,** by Professor H. A. Krebs, M.A., M.D., F.R.S.

To be given in the Chemistry Building, King's College, Newcastle-on-Tyne. All Fellows are invited.

NORTH WALES.

Thursday, May 3rd, 1951, *at* 5.45 *p.m.*

Lecture by Professor M. G. Evans, D.Sc., F.R.S.

Joint meeting with University College of North Wales Chemical Society to be held in the Department of Chemistry, University College of North Wales, Bangor.

NOTTINGHAM.

Friday, May 4th, 1951, *at* 5 *p.m.*

Centenary Lecture, **Some Recent Advances in the Chemistry of Natural Products,** by Professor R. B. Woodward (Harvard).

To be given in the Chemistry Lecture Theatre, The University, Nottingham.

SHEFFIELD.

Thursday, May 3rd, 1951, *at* 5.30 *p.m.*

Lecture, **Oxide Catalysts,** by Professor W. E. Garner, C.B.E., F.R.S.

Joint meeting with the University Chemical Society to be held in the Chemistry Lecture Theatre, The University, Sheffield.

PROCEEDINGS

OF THE

CHEMICAL SOCIETY

Minutes of a

SCIENTIFIC MEETING

held in the Science Lecture Theatre, University College, Hull, on March 1st, 1951, at 8 p.m.

MR. JOHN NICHOLSON, M.A., Principal of University College, Hull, extended a warm welcome to the Society, which was holding its first Official Meeting in Hull. MR. R. P. BELL, M.A., F.R.S., Vice-President, who was in the Chair, replied on behalf of the Society.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: J. J. Kipling, G. M. Hankinson, P. S. Johnson, N. G. Wollenberg, R. R. Baldwin, P. E. Gray, W. K. H. Lakin, A. J. Harms, R. F. Simmons, H. P. Crocker.

TILDEN LECTURE.

After a brief introduction, the Chairman called upon Professor F. S. Dainton to deliver the Tilden Lecture entitled, "Atoms and Radicals in Aqueous Solution." At the conclusion of the lecture, a vote of thanks to Professor Dainton, proposed by Professor Brynmor Jones, was carried with acclamation.

Minutes of a

SCIENTIFIC MEETING

held at Burlington House on Thursday, March 15th, 1951, at 7.30 p.m.

The President, PROFESSOR E. K. RIDEAL, M.B.E., M.A., D.Sc., F.R.S., was in the Chair.

MINUTES.

The Minutes of the Scientific Meetings held at Burlington House on February 15th, 1951, and at University College, Hull, on March 1st, 1951, were read, and were confirmed and signed.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: M. A. Champney, Norman S. Corney, J. B. Bookey, C. J. B. Fincham, W. G. Bartley, D. G. Carter, K. B. Alberman, P. W. C. Barnard, J. H. Binks, John B. Ley, D. S. P. Patterson.

SCIENTIFIC COMMUNICATIONS.

The following papers were read and discussed:

"The Chloride Ethoxides of Zirconium." By D. C. Bradley, F. M. Abd-el Halim, and W. Wardlaw.

"The Structure of Olefin Co-ordination Compounds." By J. Chatt.

"High Temperature Chemistry of the System CaO–UO_3. The Ternary System Ca–U–O." By K. B. Alberman, R. C. Blakey, and J. S. Anderson.

Minutes of a

SCIENTIFIC MEETING

held at Burlington House on Thursday, March 20th, 1951, at 4 p.m.

The President, PROFESSOR E. K. RIDEAL, M.B.E., M.A., D.Sc., F.R.S., was in the Chair.

MINUTES.

The Minutes of the Scientific Meeting held at Burlington House on March 15th, 1951, were read, and were confirmed and signed.

FORMAL ADMISSION OF FELLOWS.

The following were admitted Fellows of the Society: R. Alleyn Davison, J. Leicester, E. J. Alford, R. A. Russell, F. P. Bannister, C. J. Wilkins, D. Lawton, L. S. Adler, S. J. Pugh, A. W. Scopes, J. V. L. Longstaff, E. C. Leisegang, L. N. Short, C. J. S. M. Simpson, J. F. Allen, P. Piganiol.

PRESENTATION OF AWARDS.

The President presented the Corday–Morgan Medal and Prize for 1949 to Dr. D. H. R. Barton, the Harrison Memorial Prize for 1950 to Dr. H. C. Longuet-Higgins, and the Longstaff Medal for 1951 to Professor C. K. Ingold.

PRESIDENTIAL ADDRESS.

The President then delivered his Presidential Address entitled, "Concepts in Catalysis—The Contributions of Paul Sabatier and of Max Bodenstein." At the conclusion of the Address, a vote of thanks to the President, proposed by Professor C. K. Ingold, and seconded by Dr. A. H. Lamberton, was carried with acclamation.

OFFICIAL ANNOUNCEMENTS

DEATHS.

The Council regret to announce the deaths of the following Fellows:

	Elected.	Died.
Robert William Buttemer (Godalming)	May 3rd, 1894.	Jan. 19th, 1951.
David Brownlie (Ealing)	Feb. 15th, 1912.	Feb. 8th, 1951.
Thomas William Gibling (Sherborne) ...	May 6th, 1937.	Jan. 2nd, 1951.
James Kewley (Cheam)	Apr. 30th, 1902.	Feb. 20th, 1951.
Alan Stubbs (S.E.3)	June 15th, 1944.	Jan. 26th, 1951.
Thomas Turner (Leatherhead)	Feb. 1st, 1883.	Jan. 31st, 1951.

CONGRATULATIONS.

The President has conveyed the congratulations of the Society to the following who were elected Fellows of the Royal Society on March 15th, 1951:

Arthur Herbert Cook (Epsom).
Geoffrey Gee (Welwyn Garden City).
Harry Raymond Ing (Oxford).
Albert Neuberger (N.W.7).
James Arthur Prescott (Adelaide).
Alfred René John Paul Ubbelohde (Belfast).

ELECTION OF NEW FELLOWS.

The following 79 candidates were elected Fellows of the Society on March 15th, 1951

Ronald James Anderson.
Robert Moffat Anderson.
Gordon Barron.
Bernard Richard Bluestein.
Robert Thomas Bottle.
Joseph Brenner.
Christine Mavis Brown.
Desmond Goble Brown.
Joan Patricia Brown.
William Kerr Buchanan.
William Bullough.
Shafique Ahmad Butt.
Donald Strachan Chisholm.
Ian Ernest Climie.
Edward Alfred Clough.
Peter Cohn.
Clifford Paul Cole.
Bryan Coleby.
James Young Cooper.
Sidney Alfred Cooper.
Patrick Joseph Corish.
Robert Bowser Cundall.
Francis Stanley Davidson.
Otis Clifford Dermer.
George Herbert Dunton.
Christopher Earland.
Peter Manfrid Ellis.
Alan Challoner Fletcher.
Max Frankel.
William Charles Garratt.
Maxwell Gordon.
Francis Newton Hayes.
Stephen D. Heineman.
Patrick Robinson Huddleston.
Arthur James Huggard.
Cornelius Newbold Hunter.
Thomas Alan Ingles.
Anthony Hugh Jackson.
Gerard Forsyth Judd.
Otto Samuel Kauder.
Edward Louis King.
Margaret Gwenllian Kingston.
Terence Leonard John Lakin.
Edgar Lambert.
Walter M. Lauer.
Ronald Douglas Lewis.
William Stewart Liddle.
Gwilym Ionwy Wyn Llewelyn.
Roy McGillivray.
Norman Mackenzie.
Archibald James Ernest Moss.
Owen Eldred Mott.
Arthur Naylor.
Norman Lovelace Paddock.
Thomas Rowland Phillips.
Fausto A. Ramirez.
Jack Louis Ratner.
Peter William Redgrove.
Kenneth Gordon Reed.
Bruce Ritchie.
Peredur John Pennant Roberts.
Norman Robinson.
Thomas Gordon Rowe.
Adnam Abdul-rida Al-Sayigh.
Alan Sidle.
Maurice Silber.
Gerald Ernest Hamor Skrimshire.
Geoffrey William Smith.
Maurice John Soulal.
John Arthur Stallard.
Eric Hubert Steiner.
Kenneth Stanley Sutherland.
Hans Roderick Tietze.
Ronald George Toms.
Robert Tulip.
Adolphe Marie Alfred Walch.
Leslie Albert Whalley.
John Marshall Whitmarsh.
Ernest Roland Woodcock.

GIFTS.

Acknowledgment is made of a gift of the Society's publications from Mr. A. P. Mieras.

HUGO MÜLLER LECTURER.

Professor F. A. Paneth has been appointed Hugo Müller Lecturer for the Session 1951—1952.

TILDEN LECTURERS.

Professor C. A. Coulson and Professor D. H. Hey have been appointed Tilden Lecturers for the Session 1951—1952.

CENTENARY LECTURER.

Professor T. Reichstein has agreed to deliver a Centenary Lecture during the Session 1951—1952.

BUREAU OF ABSTRACTS.

The Society has been advised that additional Abstractors are required by the Bureau of Abstracts. Fellows who are prepared to undertake abstracting are asked to write to the Secretary of the Bureau of Abstracts, Colquhoun House, Broadwick Street, London, W.1.

MEETINGS OUTSIDE LONDON

EDINBURGH.

" Some Aspects of Infra-red Measurements," by Dr. H. W. Thompson, F.R.S.

A joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry was held in the North British Station Hotel on February 22nd, 1951, with Professor I. A. Preece in the Chair.

The lecture was delivered to a large audience, and a vote of thanks to the Lecturer, moved by Dr. Mowbray Ritchie, was carried with acclamation.

" Some Observations on Materials of Construction for Chemical Plants," by Dr. N. P. Inglis.

A joint meeting with the Royal Institute of Chemistry and the Society of Chemical Industry was held in the North British Station Hotel on March 15th, 1951, with Professor S. J. Watson in the Chair.

After the discussion which followed the lecture, a vote of thanks to the Lecturer, moved by Dr. Hoblyn, was carried with acclamation.

SHEFFIELD.

" The Chemistry of Extractives from Hardwoods," by Professor F. E. King, M.A., D.Phil.

A joint meeting with the University Chemical Society was held in the Chemistry Lecture Theatre on March 1st, 1951, with Professor R. D. Haworth in the Chair.

After pointing out that the resistance of timber to decay depended upon the presence of fungi-toxic compounds in the heartwood, Professor King gave an account of the investigation of the structures of chlorophorin (a geranyl-tetrahydroxy-stilbene) and of baikiarin (a tetrahydropicolinic acid). On the motion of Dr. A. H. Lamberton, a cordial vote of thanks was given to the Lecturer.

SOUTHAMPTON.

" What is a Chemical Bond? " by Professor C. A. Coulson, M.A., D.Sc., F.R.S.

A joint meeting with the Chemical Society of University College, Southampton, was held in the Physics Department of University College, Southampton, on February 23rd, 1951, with Mr. R. E. Parker in the Chair.

Professor Coulson discussed fundamental characteristics of the chemical bond, stressing in particular, the importance of maximum overlap of orbitals in bond formation. The lecture was illustrated by slides.

After a discussion, a vote of thanks to Professor Coulson, proposed by Mr. E. Cartmell, was carried with acclamation.

LIST OF APPLICATIONS FOR FELLOWSHIP

(*Fellows wishing to lodge objection to the election of these candidates should communicate with the Honorary Secretaries within ten days of the date of publication of the* Journal *for April*, 1951. *Such objections will be treated as confidential. The forms of application are available in the Library.*)

***Abramovitch, Rudolph Abraham Haim,** B.Sc. (Lond. and Farouk 1st Univ.). Rumanian. 9, Rue du Musee, Alexandria, Egypt. Teacher, Menasce Secondary School. *Signed by:* J. Kenyon, Nazim Fakhoury, Youssef Iskandar.

***Anderson, Robert Craig,** B.Sc. (Glas.), A.R.I.C. British. Whang House, Beith, Ayrshire. Research Student, Royal Technical College, Glasgow. *Signed by:* John McLean, William Dawson, Robert Stevenson.

***Angyal, Charles Leslie,** B.Sc. (Sydney). Hungarian. 22, Ocean Avenue, Double Bay, Sydney, N.S.W. Demonstrator, University of Sydney. *Signed by:* T. Iredale, S. J. Angyal, H. C. Freeman.

Avonda, Frank Peter, B.S. (City Coll. of New York), A.M. (Columbia). American. Chemistry Department, Ohio State University, Columbus 10, Ohio, U.S.A. Graduate Student. *Signed by:* Christopher L. Wilson, Melvin S. Newman, Maxwell Nager.

Bache, Herbert Josiah, A.R.I.C. British. Hurst Lodge, Bridgewater Road, Weybridge. Chief Chemist, Electrochemical Engineering Co., Ltd. *Signed by:* W. E. Wright, C. R. Draper, G. Schmerling.

Baker, Guy Houghton. British. 67, Lichfield Grove, Finchley, N.3. Assistant Chemist, Whitbread & Co., Ltd., E.C.1. *Signed by:* E. Barton Wright, G. Harris, N. S. Curtis.

***Barnard, Edgar John.** British. 51, Evelyn Crescent, Shirley, Southampton. Research Student, University College, Southampton. *Signed by:* K. R. Webb, E. Cartmell, A. R. Burkin.

***Bird, Ronald Frederick,** B.Sc. (Lond.). British. 82, Pentney Road, Balham, S.W.12. Research Student. *Signed by:* E. E. Turner, J. W. Smith, G. R. Hilldrith.

***Blackhall, Alexander,** B.Sc. (Aberd.), A.R.I.C. British. Bendoran, Tarland, Aberdeenshire. Research Student. *Signed by:* R. H. Thomson, R. M. Barrer, A. M. Meston.

Bloom, Edward, M.Sc. (Cantab), Ph.D. (Lond.), A.R.I.C. British. 14, Upney Lane, Barking, Essex. Senior Assistant in Chemistry, South-East Essex Technical College, Dagenham. *Signed by:* J. D. Kendall, D. Ridge, J. Ratcliffe.

Bolsover, Kenneth, A.R.I.C. British. Woodside, Duffield Lane, Stoke Poges. Chief Chemist, Chappie, Ltd., Slough. *Signed by:* A. A. Houghton, E. I. Beeching, H. J. T. Ellingham.

Boulter, Norman, B.Sc. (Manc.). British. 88, Field Lane, Alvaston, Derby. Works Chemist, British Celanese, Ltd. *Signed by:* E. R. H. Jones, H. B. Henbest, T. G. Halsall.

Bowcott, John Edward Llewellyn, B.Sc. (Reading), A.R.I.C. British. 53, Alexandra Road, Reading, Berks. Research Student, University of Reading. *Signed by:* Paul F. Holt, J. E. Price, D. T. King.

***Bowyer, Freda,** B.Sc. (Lond.). British. Royal Holloway College, Englefield Green, Surrey. Research Student. *Signed by:* Kathleen Mackay, T. G. Bonner, K. Singer.

Brown, Desmond Goble, B.Sc. (N.Z.). British. 30, Chapman Street, Kaikorai, Dunedin N.W.2, New Zealand. Student, Otago University. *Signed by:* F. G. Soper, W. T. Fyfe, A. D. Campbell.

***Brown, Joseph Clair,** B.Sc. (Lond.), A.R.I.C. British. 95, Seymour Road South, Clayton, Manchester, 11. Chemist-Colourist, Clayton Aniline Co. *Signed by:* G. Spencer, J. H. Dent, E. Shaw.

Brown, William Orr, B.Sc. and M. Agric. (Q.U.B.), A.R.I.C. British. Chemical Research Division, Ministry of Agriculture, Queen's University, Belfast. Scientific Officer and Assistant Lecturer in Agriculture. *Signed by:* H. Graham, K. L. Robinson, W. Honneyman.

Bryson, Joseph Lindsay, A.R.I.C. British. Heatherlea, Weston Road, Runcorn, Cheshire. Works Investigation Chemist. *Signed by:* F. Rumford, William Gibb, W. Anderson.

Burns, Harold Halsall, B.Sc. (Dunelm). British. 1, Welbourne Road, Liverpool, 16. Research Student. *Signed by:* John E. Gregory, J. H. Wilkinson, Joseph Gibson.

***Bye, Gerald Charles,** British. 6A, Kings Parade, High Street, Barkingside, Ilford. Research Student. *Signed by:* S. J. Gregg, R. King, H. T. S. Britton.

***Cadogan, John Ivan George.** British. 112, Central Street, London, E.C.1. Research Student, King's College, London. *Signed by:* S. H. Harper, P. J. Hillson, A. J. B. Robertson.

***Capon, Brian,** British. 234, Charminster Road, Bournemouth. Research Student, University College, Southampton. *Signed by:* K. R. Webb, A. R. Burkin, E. Cartmell.

Capper, Kenneth Roy, B.Pharm. and Ph.D. (Lond.), Ph.C., D.I.C. British. The Pharmaceutical Society, 17, Bloomsbury Square, London, W.C.1. Editor, Scientific Publications. *Signed by:* W. H. Linnell, H. Burton, H. H. Hodgson.

***Carter, Richard Jeremy Lorains.** Briti h. The White House, Swithland, Loughborough, Leics. Research Student. *Signed by:* W. A. Waters, G. D. Parkes, L. J. Goldsworthy.

Case, Albert Cecil, B.Sc. (Lond.), A.R.I.C. British. Messrs. Whitbread and Co., Ltd., The Brewery, Chiswell Street, London, E.C.1. Chemist. *Signed by:* G. Harris, E. Barton Wright, J. T. G. Johnson.

***Clarke, Stanley Arthur.** British. 125, Abbotts Road, Mitcham, Surrey. Chemist. *Signed by:* G. M. Hamilton, P. J. Killingback, K. I. Speed.

***Cleaver, Alan John,** B.Sc. (Birm.). British. 138, Middlemore Road, Northfield, Birmingham, 31. Research Student, University of Birmingham. *Signed by:* L. L. Bircumshaw, W. G. Overend, M. Stacey.

***Cole, Robert Lynn.** British. Keble College, Oxford. Research Student. *Signed by:* W. A. Waters, H. Irving, J. C. Smith.

***Collins, Harold John,** B.Sc. (Lond.). A.R.I.C. British. 17, The Leazes, Newburn, Northumberland. Research Chemist, International Paints Ltd., Gateshead. *Signed by:* J. O. Harris, D. G. Felton, H. J. Vipond.

***Cottrell, Anthony Morris,** B.Sc. (Lond.), A.R.I.C. British. 3, Highfield Close, Duxford, Cambs. Chemist, Linoleum Manufacturing Co. Ltd., Staines. *Signed by:* G. G. Pullen, G. J. L. Griffin, D. C. Beese.

Coulson, Roland Edwin, A.R.I.C. British. Devon House, 134, Manor Road, Fishponds, Bristol. Research Chemist. *Signed by:* A. J. Edwards, S. W. R. Morgan, A. K. Barbour.

Craddock, Edward Basil. British. 18, King Edward Avenue, Aylesbury, Bucks. Engineer and General Manager, Aylesbury and District Gas Undertaking. *Signed by:* W. Hodkinson, T. C. Battersby, C. D. Birks.

***Crawshaw, Allan,** B.Sc. (Lond.). British. 1, Swindon Street, Burnley. Research Student, Manchester University. *Signed by:* M. C. Whiting, T. H. Quibell, H. B. Henbest.

Davies, Albert Gruffydd, B.Sc. (Wales). British. Edward Davies Chemical Laboratories, Buarth, Aberystwyth. Research Student. *Signed by:* C. W. Davies, C. Monk, Mansel Davies.

Davis, Arthur Leslie, A.R.I.C. British. Treatment Plant Laboratory, Southend Waterworks Co., Ulting, Maldon, Essex. Chief Chemist. *Signed by:* G. U. Houghton, T. H. Morton, J. H. MacGregor, R. W. Richardson.

***De Villiers, Jean Pierre,** B.Sc. (Pretoria). South African. 752, Park Street, Pretoria, South Africa. Research Student, Pretoria University. *Signed by:* D. A. Sutton, A. M. Stephen, J. R. Nunn.

Dorfman, Edwin, B.S. (Penn. State College), A.M. (Columbia). American. 1440, Lexington Avenue New York 20, New York, U.S.A. Research Student, Columbia University. *Signed by:* William von E. Doering, David Curtin, Kenneth B. Wiberg.

***Duncanson, Leonard Andrew,** B.Sc. and Ph.D. (Lond.). British. I.C.I. Butterwick Research Laboratories, The Frythe, Welwyn, Herts. Research Chemist. *Signed by:* Ernst Vischer, James S. Moffatt, J. F. Grove.

***Dunn, Alexander Simpson,** B.Sc. (Aberd.), A.R.I.C. British. Chemistry Department, The University, Edgbaston, Birmingham 15. Research Student. *Signed by:* H. W. Melville, J. C. Robb, P. R. E. Cowley.

***Elliott, David John,** B.Sc. (Lond.). British. 6, Reddish Avenue, Whaley Bridge, Via Stockport. Assistant Works Chemist, Paper Manufacturing Company. *Signed by:* S. G. Lawrence, H. H. Armstrong, T. P. Nevell.

Fawcett, Cyril Herbert, B.Sc. (Lond.). British. Robsacks, Wye, Nr. Ashford, Kent. Research Assistant, Wye College. *Signed by:* R. L. Wain, E. D. Hughes, C. K. Ingold.

Firth, William Crompton, B.A. (Oxon). British. Cottingley, Ballard Road, Swanage, Dorset. Research Student. *Signed by:* W. A. Waters, K. W. Bentley, A. S. Bailey.

***Fletcher, Norman William,** B.Sc. (Lond.), A.R.I.C. British. c/o Greengarth Hall, Holmrook, Cumberland. Chemist, Ministry of Supply, Sellafield. *Signed by:* M. F. Sheppard, F. J. Armson, G. A. Welch.

Flockhart, Brian Duncan, M.Sc. (Q.U.B.), A.R.I.C. British. 86, My Lady's Road, Belfast. Assistant Lecturer in Chemistry, Queen's University, Belfast. *Signed by:* R. C. Pink, R. G. R. Bacon, H. Graham.

***Gailey, Robert McNaught,** B.Sc. (Glas.). British. 80, Blackstoun Oval, Paisley. Research Student. *Signed by:* James D. Loudon, Ralph A. Raphael, A. F. McColl.

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PAPERS RECEIVED

(List of papers received between February 17th and March 17th, 1951.)

"Chemical studies on 2 : 3-bis-*p*-dimethylaminophenylbutane-2 : 3-diol." By MILTON J. ALLEN.

"Synthetic antimalarials. Part XLVII. N^1-3 : 4-Dihalogenophenyl-N^5-alkyl- and -dialkyldiguanides." By A. F. CROWTHER, (the late) F. H. S. CURD, D. G. DAVEY, J. A. HENDRY, W. HEPWORTH, and F. L. ROSE.

"Synthetic antimalarials. Part XLVIII. The action of halogens on N^1-aryldiguanides." By A. F. CROWTHER, (the late) F. H. S. CURD, and F. L. ROSE.

"The dissociation constants of the cupric salts of some monocarboxylic acids." By (MISS) M. LLOYD, V. WYCHERLEY, and C. B. MONK.

"Studies on fructosans. Part III. A fructosan from *Lolium perenne*." By R. A. LAIDLAW, and S. G. REID.

"The polarographic reduction of some aminoacridines." By R. C. KAYE and H. I. Stonehill.

"Ultra-violet absorption spectra of some derivatives of quinoline, quinazoline, and cinnoline." By (MISS) J. M. HEARN, R. A. MORTON, and J. C. E. SIMPSON.

"Spectrophotometric determinations of the second dissociation constant (as pK_a) of 5-aminoquinoline and 6-aminoquinoline." By (MISS) J. M. HEARN, R. A. MORTON, and J. C. E. SIMPSON.

"Comparisons of ultra-violet absorption spectra and chemical properties in the quinoline, quinazoline, and cinnoline series." By (MISS) J. M. HEARN, R. A. MORTON, and J. C. E. SIMPSON.

"The Friedel–Crafts reaction of fluoranthene." By N. CAMPBELL, W. K. LEADILL, and J. F. K. WILSHIRE.

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"Wool wax. Part I. Synthesis of some *anteiso*-acids." By J. R. NUNN.

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"The kinetics of the dehydrochlorination of substituted hydrocarbons. Part VII. The mechanism of the thermal decompositions of 1 : 1 : 2 : 2- and 1 : 1 : 1 : 2-tetrachloroethane." By D. H. R. BARTON and K. E. HOWLETT.

"The kinetics of the dehydrochlorination of substituted hydrocarbons. Part VIII. The mechanisms of the thermal decompositions of 1-chloropropane, 1-chlorobutane, and 2 : 2′-dichlorodiethyl ether." By D. H. R. BARTON, A. J. HEAD, and R. J. WILLIAMS.

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